Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases

https://t.me/MBS_MedicalBooksStore

John E. Bennett
Raphael Dolin
Martin J. Blaser

Ninth Edition

ELSEVIER

Mandell, Douglas, and Bennett's

Principles and Practice of Infectious Diseases

John E. Bennett, MD

Adjunct Professor of Medicine
Uniformed Services University of the Health Sciences
F. Edward Hebert School of Medicine
Bethesda, Maryland

Raphael Dolin, MD

Maxwell Finland Professor of Medicine (Microbiology and Molecular Genetics)
Harvard Medical School;
Attending Physician
Beth Israel Deaconess Medical Center;
Brigham and Women's Hospital
Boston, Massachusetts

Martin J. Blaser, MD

Henry Rutgers Chair of the Human Microbiome
Professor of Medicine and Microbiology—RWJMS
Director, Center for Advanced Biotechnology and Medicine
Rutgers University
Piscataway, New Jersey

Ninth Edition

https://t.me/MBS_MedicalBooksStore

ELSEVIER

Elsevier
1600 John F. Kennedy Blvd.
Ste 1600
Philadelphia, PA 19103-2899

MANDELL, DOUGLAS, AND BENNETT'S PRINCIPLES AND PRACTICE OF INFECTIOUS DISEASES, NINTH EDITION ISBN: 978-0-323-48255-4
Copyright © 2020 by Elsevier, Inc. All rights reserved.

The chapters listed below are in the public domain:
- Cell-Mediated Defense Against Infection by Michail S. Lionakis and Tobias M. Hohl
- Granulocytic Phagocytes by Frank R. DeLeo and William M. Nauseef
- Drugs for Protozoal Infections Other Than Malaria by James S. McCarthy, Glenn W. Wortmann, and Louis V. Kirchhoff
- Foodborne Disease by Karen K. Wong and Patricia M. Griffin
- The Immunology of Human Immunodeficiency Virus Infection by Susan Moir, Mark Connors, and Anthony S. Fauci
- Pediatric Human Immunodeficiency Virus Infection by Geoffrey A. Weinberg and George K. Siberry
- Introduction to Herpesviridae by Jeffrey I. Cohen
- Human Herpesvirus Types 6 and 7 (Exanthem Subitum) by Jeffrey I. Cohen
- Herpes B Virus by Jeffrey I. Cohen
- Plague *(Yersinia pestis)* by Paul S. Mead
- *Trypanosoma* Species (American Trypanosomiasis, Chagas Disease): Biology of Trypanosomes by Louis V. Kirchhoff
- Agents of African Trypanosomiasis (Sleeping Sickness) by Louis V. Kirchhoff
- *Toxoplasma gondii* by José G. Montoya, John C. Boothroyd, and Joseph A. Kovacs
- *Giardia lamblia* by Theodore E. Nash and Luther A. Bartelt
- Visceral Larva Migrans and Other Uncommon Helminth Infections by Theodore E. Nash
- Infections Caused by Percutaneous Intravascular Devices by Susan E. Beekmann and David K. Henderson
- Transfusion- and Transplantation-Transmitted Infections by Sridhar V. Basavaraju and Matthew J. Kuehnert

No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopying, recording, or any information storage and retrieval system, without permission in writing from the publisher. Details on how to seek permission, further information about the Publisher's permissions policies and our arrangements with organizations such as the Copyright Clearance Center and the Copyright Licensing Agency, can be found at our website: www.elsevier.com/permissions.

This book and the individual contributions contained in it are protected under copyright by the Publisher (other than as may be noted herein).

Notice

Practitioners and researchers must always rely on their own experience and knowledge in evaluating and using any information, methods, compounds or experiments described herein. Because of rapid advances in the medical sciences, in particular, independent verification of diagnoses and drug dosages should be made. To the fullest extent of the law, no responsibility is assumed by Elsevier, authors, editors or contributors for any injury and/or damage to persons or property as a matter of products liability, negligence or otherwise, or from any use or operation of any methods, products, instructions, or ideas contained in the material herein.

Previous editions copyrighted 2015, 2010, 2005, 2000, 1995, 1990, 1985, and 1979.

Library of Congress Control Number: 2019944671

https://t.me/MBS_MedicalBooksStore

Publishing Director: Dolores Meloni
Senior Content Strategist: Charlotta Kryhl
Senior Content Development Manager: Lucia Gunzel
Publishing Services Manager: Catherine Jackson
Book Production Specialist: Kristine Feeherty
Design Direction: Amy Buxton

Printed in Canada

Last digit is the print number: 9 8 7 6 5 4 3 2 1

ELSEVIER Book Aid International Working together to grow libraries in developing countries
www.elsevier.com • www.bookaid.org

Contributors

Kjersti Aagaard, MD, PhD
Henry and Emma Meyer Chair in Obstetrics and Gynecology, Professor and Vice Chair of Research, Department of Obstetrics and Gynecology, Division of Maternal-Fetal Medicine, Baylor College of Medicine and Texas Children's Hospital, Houston, Texas
The Human Microbiome of Local Body Sites and Their Unique Biology

Marie Abdallah, MD
Medical Director HIV Services, Ambulatory Care, Kings County Hospital; Infectious Disease Specialist, Infectious Disease, SUNY Downstate Medical Center, Brooklyn, New York
Vulvovaginitis and Cervicitis

Fredrick M. Abrahamian, DO
Health Sciences Clinical Professor of Emergency Medicine, David Geffen School of Medicine at UCLA, Los Angeles, California; Faculty, Department of Emergency Medicine, Olive View-UCLA Medical Center, Sylmar, California
Bites

Shruti Agnihotri, MD
Department of Neurology, University of Alabama at Birmingham, Birmingham, Alabama
Neurologic Diseases Caused by Human Immunodeficiency Virus Type 1 and Opportunistic Infections

Sana S. Ahmed, MD
Medical Epidemiologist, Communicable Diseases, Lake County Health Department and Community Health Center, Waukegan, Illinois
Endemic Treponematoses

Ban Mishu Allos, MD
Associate Professor, Department of Medicine, Division of Infectious Diseases, Vanderbilt University School of Medicine, Nashville, Tennessee
Campylobacter jejuni *and Related Species*

Saleh A. Alqahtani, MD
Medical Director of International Digestive and Liver, Department of Medicine, Johns Hopkins Hospital, Baltimore, Maryland
Gastrointestinal, Hepatobiliary, and Pancreatic Manifestations of Human Immunodeficiency Virus Infection

Jeffrey L. Anderson, MD
Distinguished Clinical and Research Physician, Cardiovascular Department, Intermountain Medical Center Heart Institute; Professor of Medicine, Internal Medicine (Cardiovascular), University of Utah School of Medicine, Salt Lake City, Utah
Myocarditis and Pericarditis

David R. Andes, MD
Professor of Medicine, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin
Cephalosporins

Jason R. Andrews, MD
Assistant Professor, Infectious Diseases and Geographic Medicine, Stanford University School of Medicine, Stanford, California
Typhoid Fever, Paratyphoid Fever, and Typhoidal Fevers

Fred Y. Aoki, MD
Professor, Departments of Medicine, Medical Microbiology & Infectious Diseases, and Pharmacology & Therapeutics, University of Manitoba, Winnipeg, Manitoba, Canada
Antiviral Drugs for Influenza and Other Respiratory Virus Infections
Antivirals Against Herpesviruses

Michael A. Apicella, MD
Professor, Microbiology and Internal Medicine, The University of Iowa, Iowa City, Iowa
Neisseria gonorrhoeae *(Gonorrhea)*

Rafael Araos, MD, MMSc
Assistant Professor of Medicine, Facultad de Medicina Clinica Alemana Universidad del Desarrollo; Millennium Nucleus for Collaborative Research on Antimicrobial Resistance (MICROB-R), Santiago, Chile
Pseudomonas aeruginosa *and Other* Pseudomonas *Species*

Kevin L. Ard, MD, MPH
Director, Sexual Health Clinic, Infectious Disease Division, Massachusetts General Hospital, Boston, Massachusetts
Pulmonary Manifestations of Human Immunodeficiency Virus Infection

Cesar A. Arias, MD, MSc, PhD
Professor of Medicine, Microbiology, and Molecular Genetics, Herbert L. and Margaret W. DuPont Chair in Infectious Diseases, Laurel and Robert H. Graham Faculty Fellow at McGovern Medical School, Director, Center for Antimicrobial Resistance and Microbial Genomics, Director, Center for Infectious Diseases, School of Public Health, University of Texas Health Science Center at Houston, Houston, Texas
Daptomycin and Quinupristin-Dalfopristin
Glycopeptides (Vancomycin and Teicoplanin) and Lipoglycopeptides (Telavancin, Oritavancin, and Dalbavancin)
Enterococcus *Species,* Streptococcus gallolyticus *Group, and* Leuconostoc *Species*

David M. Aronoff, MD
Director, Division of Infectious Diseases, Department of Medicine, Vanderbilt University Medical Center, Nashville, Tennessee
Metronidazole
Macrolides and Clindamycin

Naomi E. Aronson, MD
Director, Infectious Diseases Division, Professor, Department of Medicine, Uniformed Services University of the Health Sciences, Bethesda, Maryland
Leishmania *Species: Visceral (Kala-Azar), Cutaneous, and Mucosal Leishmaniasis*

Michael H. Augenbraun, MD
Professor of Medicine, Chief, Division of Infectious Diseases, Department of Medicine, SUNY Downstate Medical Center, Brooklyn, New York
Urethritis
Vulvovaginitis and Cervicitis
Genital Skin and Mucous Membrane Lesions

Paul G. Auwaerter, MD
Sherrilyn and Ken Fisher Professor of Medicine, Clinical Director, Division of Infectious Diseases, Johns Hopkins University School of Medicine, Baltimore, Maryland
Francisella tularensis *(Tularemia)*

Francisco Averhoff, MD, MPH
Division of Viral Hepatitis, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, Centers for Disease Control and Prevention, Atlanta, Georgia
Hepatitis A Virus

Dimitri T. Azar, MD, MBA
Clinical Lead, Ophthalmology Programs and Senior Director of Ophthalmic Innovations, Alphabet Verily Life Sciences; Distinguished University Professor, Former Medical School Dean, and BA Field Chair of Ophthalmological Research, University of Illinois College of Medicine, Chicago, Illinois
Microbial Keratitis
Microbial Conjunctivitis

Tara M. Babu, MD, MSCI
Assistant Professor of Medicine, Infectious Diseases Division, University of Rochester School of Medicine and Dentistry, Rochester, New York
Urethritis

Laura Hinkle Bachmann, MD, MPH
Professor, Internal Medicine/Infectious Diseases, Wake Forest University Health Sciences, Winston-Salem, North Carolina
Trichomonas vaginalis

Larry M. Baddour, MD
Professor of Medicine, Mayo Clinic College of Medicine; Emeritus, Infectious Diseases, Mayo Clinic, Rochester, Minnesota
Prosthetic Valve Endocarditis
Infections of Nonvalvular Cardiovascular Devices

Lindsey R. Baden, MD
Associate Professor of Medicine, Harvard Medical School; Associate Physician, Director of Clinical Research (Division of Infectious Diseases), Director of Transplant Infectious Diseases, Brigham and Women's Hospital; Director of Infectious Diseases, Dana-Farber Cancer Institute, Boston, Massachusetts
Epidemiology and Prevention of AIDS and HIV Infection, Including Preexposure Prophylaxis and HIV Vaccine Development

Carol J. Baker, MD
Professor of Pediatrics, Department of Pediatrics, Division of Infectious Diseases, University of Texas McGovern Medical School, Houston, Texas
Streptococcus agalactiae *(Group B Streptococci)*

Sarah-Blythe Ballard, MD, PhD, MPH
Epidemic Intelligence Service, Centers for Disease Control and Prevention, Atlanta, Georgia
Applied Epidemiology for the Infectious Diseases Physician

Gerard R. Barber, RPh, MPH
Department of Pharmacy Services, University of Colorado Hospital, University of Colorado, Skaggs School of Pharmacy & Pharmaceutical Sciences, Aurora, Colorado
Unique Antibacterial Agents

Scott D. Barnes, MD
Chief, Warfighter Refractive Eye Surgery Clinic, Womack Army Medical Center, Fort Bragg, North Carolina
Microbial Keratitis
Microbial Conjunctivitis

Dan H. Barouch, MD, PhD
Professor of Medicine, Harvard Medical School; Ragon Institute of MGH, MIT, and Harvard; Director, Center for Virology and Vaccine Research, Beth Israel Deaconess Medical Center, Boston, Massachusetts
Adenoviruses
Epidemiology and Prevention of AIDS and HIV Infection, Including Preexposure Prophylaxis and HIV Vaccine Development

Alan D. Barrett, PhD
Director, Sealy Institute for Vaccine Sciences; Professor, Department of Pathology; Professor, Department of Microbiology and Immunology, University of Texas Medical Branch, Galveston, Texas
Flaviviruses (Dengue, Yellow Fever, Japanese Encephalitis, West Nile Encephalitis, Usutu Encephalitis, St. Louis Encephalitis, Tick-Borne Encephalitis, Kyasanur Forest Disease, Alkhurma Hemorrhagic Fever, Zika)

Miriam Baron Barshak, MD
Assistant Professor of Medicine, Harvard Medical School; Associate Physician, Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts
Pancreatic Infection

Luther A. Bartelt, MD
Assistant Professor, Infectious Diseases and Global Health, The University of North Carolina at Chapel Hill, Chapel Hill, North Carolina
Giardia lamblia
Diarrhea With Little or No Fever

Sridhar V. Basavaraju, MD
Director, Office of Blood, Organ, and Other Tissue Safety, Division of Healthcare Quality Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia
Transfusion- and Transplantation-Transmitted Infections

Byron E. Batteiger, MD
Professor of Medicine, Microbiology, and Immunology, Division of Infectious Diseases, Indiana University School of Medicine, Indianapolis, Indiana
Chlamydia trachomatis *(Trachoma and Urogenital Infections)*

Stephen G. Baum, MD
Professor of Medicine, Microbiology, and Immunology, Albert Einstein College of Medicine, Bronx, New York
Mumps Virus

Arnold S. Bayer, MD
Professor of Medicine, Department of Internal Medicine, David Geffen School of Medicine at UCLA, Los Angeles, California; Associate Chief, Adult Infectious Diseases, Department of Internal Medicine, Harbor-UCLA Medical Center; Senior Investigator, St. John's Cardiovascular Research Center, Los Angeles Biomedical Research Institute, Torrance, California
Endocarditis and Intravascular Infections

J. David Beckham, MD
Associate Professor, Division of Infectious Diseases, Departments of Medicine and Neurology; Director, Infectious Disease Fellowship Training Program, University of Colorado School of Medicine, VA Rocky Mountain Regional Medical Center, Aurora, Colorado
Encephalitis

Susan E. Beekmann, RN, MPH
University of Iowa Carver College of Medicine, Iowa City, Iowa
Infections Caused by Percutaneous Intravascular Devices

Richard H. Beigi, MD, MSc
Professor, Reproductive Sciences, Department of Obstetrics, Gynecology and Reproductive Sciences, Chief Medical Officer and VP of Medical Affairs, Magee Womens Hospital of UPMC, Pittsburgh, Pennsylvania
Infections of the Female Pelvis

John E. Bennett, MD
Adjunct Professor of Medicine, Uniformed Services University of the Health Sciences, F. Edward Hebert School of Medicine, Bethesda, Maryland
Chronic Meningitis
Introduction to Mycoses

Elie F. Berbari, MD
Professor of Medicine, Department of Infectious Diseases, Mayo Clinic, Rochester, Minnesota
Osteomyelitis

Joseph S. Bertino, Jr., PharmD
Associate Professor of Pharmacology, College of Physicians and Surgeons, Columbia University, New York; Editor-in-Chief, The Journal of Clinical Pharmacology; New York Principal, Bertino Consulting, Schenectady, New York
Tables of Antiinfective Agent Pharmacology
Pharmacokinetics and Pharmacodynamics of Antiinfective Agents

Adarsh Bhimraj, MD
Head, Neuroinfections, Section of Neurological Infectious Diseases, Cleveland Clinic, Cleveland, Ohio
Cerebrospinal Fluid Shunt and Drain Infections

Torrey Boland Birch, MD
Assistant Professor, Department of Neurological Sciences, Rush University Medical Center, Chicago, Illinois
Tetanus (Clostridium tetani)
Botulism (Clostridium botulinum)

Holly H. Birdsall, MD, PhD
Senior Medical Officer, Office of Research and Development, Department Veterans Affairs, Washington, DC; Professor, Otolaryngology, Immunology and Psychiatry, Baylor College of Medicine, Houston, Texas
Adaptive Immunity: Antibodies and Immunodeficiencies

Brian G. Blackburn, MD
Clinical Assistant Professor and Fellowship Program Director, Stanford University School of Medicine; Attending Physician, Department of Internal Medicine, Division of Infectious Diseases and Geographic Medicine, Stanford Hospital and Clinics, Stanford, California
Free-Living Amebae

Lucas S. Blanton, MD
Assistant Professor, Department of Internal Medicine, Division of Infectious Diseases, Galveston, Texas
Rickettsia rickettsii *and Other Spotted Fever Group Rickettsiae (Rocky Mountain Spotted Fever and Other Spotted Fevers)*
Rickettsia prowazekii *(Epidemic or Louse-Borne Typhus)*
Rickettsia typhi *(Murine Typhus)*

Martin J. Blaser, MD
Henry Rutgers Chair of the Human Microbiome, Professor of Medicine and Microbiology—RWJMS, Director, Center for Advanced Biotechnology and Medicine, Rutgers University, Piscataway, New Jersey
Introduction to Bacteria and Bacterial Diseases
Helicobacter pylori *and Other Gastric* Helicobacter *Species*
Campylobacter jejuni *and Related Species*

David L. Blazes, MD, MPH
Global Health Division, Bill and Melinda Gates Foundation, Seattle, Washington
Applied Epidemiology for the Infectious Diseases Physician

Thomas P. Bleck, MD, MCCM
Professor of Neurology, Northwestern University Feinberg School of Medicine; Professor Emeritus of Neurological Sciences, Neurosurgery, Medicine, and Anesthesiology, Rush Medical College, Chicago, Illinois
Tetanus (Clostridium tetani)
Botulism (Clostridium botulinum)
Rabies (Rhabdoviruses)

Nicole M.A. Blijlevens, MD, PhD
Consultant and Lecturer, Department of Haematology, Radboud University Medical Centre, Nijmegen, The Netherlands
Infections in the Immunocompromised Host: General Principles

Dana M. Blyth, MD
Assistant Professor, Department of Medicine, Infectious Disease Service, Uniformed Services, University of the Health Sciences, Bethesda, Maryland; Associate Program Director, Transitional Year Program, San Antonio Uniformed Services Health Education, Consortium, San Antonio, Texas
Burns

Andrea K. Boggild, MD, MSc
Medical Director, Tropical Disease Unit, Toronto General Hospital; Associate Professor, Department of Medicine, University of Toronto; Parasitology Lead Public Health Ontario Laboratory, Toronto, Ontario, Canada
Infections in Returning Travelers

Isaac I. Bogoch, MD
Associate Professor, Infectious Diseases, University of Toronto; Consultation Physician, Infectious Diseases, Toronto General Hospital, Toronto, Ontario, Canada
Cyclospora cayetanensis, Cystoisospora belli, Sarcocystis *Species*, Balantidium coli, *and* Blastocystis *Species*

William Bonnez, MD
Professor Emeritus of Medicine, Department of Medicine, Division of Infectious Diseases, University of Rochester School of Medicine and Dentistry, Rochester, New York
Papillomaviruses

John C. Boothroyd, MD
Professor of Microbiology and Immunology, Stanford University School of Medicine, Stanford, California
Toxoplasma gondii

Luciana L. Borio, MD
Director for Medical and Biodefense Preparedness Policy, National Security Council, Washington, DC
Bioterrorism: An Overview

Patrick J. Bosque, MD
Associate Professor, Department of Neurology, University of Colorado Denver School of Medicine; Chief, Neurology Division, Department of Medicine, Denver Health Medical Center, Denver, Colorado
Prions and Prion Disease of the Central Nervous System (Transmissible Neurodegenerative Diseases)

Christopher R. Braden, MD
Deputy Director, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia
Emerging and Reemerging Infectious Disease Threats

Angela R. Branche, MD
Assistant Professor of Medicine, Department of Medicine, Division of Infectious Diseases, University of Rochester School of Medicine, Rochester, New York
Human Metapneumovirus

William J. Britt, MD
Charles Alford Professor of Pediatrics, Department of Pediatrics, Microbiology, and Neurobiology, University of Alabama School of Medicine, University of Alabama in Birmingham, Birmingham, Alabama
Cytomegalovirus

Itzhak Brook, MD
Professor of Pediatrics, Georgetown University School of Medicine, Washington, DC
Tetracyclines, Glycylcyclines, and Chloramphenicol

Matthijs C. Brouwer, MD, PhD
Neurologist, Department of Neurology, Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands
Acute Meningitis

Kevin E. Brown, MD
Consultant Medical Virologist, Virus Reference Department, Centre for Infections, Health Protection Agency, London, United Kingdom
Human Parvoviruses, Including Parvovirus B19V and Human Bocaparvoviruses

Patricia Brown, MD
Associate Professor of Medicine, Department of Internal Medicine, Division of Infectious Diseases, Wayne State University School of Medicine; Corporate Vice President of Quality and Patient Safety, Detroit Medical Center, Detroit, Michigan
Urinary Tract Infections
Infections in Injection Drug Users

Barbara A. Brown-Elliott, MS, MT(ASCP)SM
Associate Professor of Microbiology, Supervisor, Mycobacteria/Nocardia Laboratory, University of Texas Health Science Center, Tyler, Texas
Infections Caused by Nontuberculous Mycobacteria Other Than Mycobacterium avium *Complex*

Roberta L. Bruhn, MS, PhD
Co-Director, Department of Epidemiology, Vitalant Research Institute; Adjunct Assistant Professor, Department of Laboratory Medicine, University of California, San Francisco, California
Human T-Cell Leukemia Viruses (HTLV-1, HTLV-2)

Amy E. Bryant, PhD
Affiliate Professor of Medicine, University of Washington, Seattle, Washington
Streptococcus pyogenes

Eileen M. Burd, PhD
Associate Professor, Pathology and Laboratory Medicine, Emory University School of Medicine; Director, Clinical Microbiology, Emory University Hospital, Atlanta, Georgia
Other Gram-Negative and Gram-Variable Bacilli

Jane C. Burns, MD
Professor of Pediatrics, University of California San Diego, La Jolla, California
Kawasaki Disease

Larry M. Bush, MD, FACP
Affiliated Associate Professor of Medicine, University of Miami-Miller School of Medicine/JFK, Medical Center, Palm Beach County, Florida; Affiliated Professor of Medicine, Charles E. Schmidt School of Medicine/Florida Atlantic University, Boca Raton, Florida
Peritonitis and Intraperitoneal Abscesses

Arturo Casadevall, MD, PhD
Chair of the Department of Molecular Microbiology and Immunology and Professor of Medicine, Molecular Microbiology and Immunology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland
Adaptive Immunity: Antibodies and Immunodeficiencies

Mary T. Caserta, MD
Professor, Department of Pediatrics, University of Rochester School of Medicine and Dentistry, Rochester, New York
Pharyngitis
Acute Laryngitis

Elio Castagnola, MD
Infectious Disease Unit, Istituto Giannina Gaslini, Genova, Italy
Prophylaxis and Empirical Therapy of Infection in Cancer Patients

Richard E. Chaisson, MD
Professor of Medicine, Epidemiology, and International Health, Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland
General Clinical Manifestations of Human Immunodeficiency Virus Infection (Including Acute Retroviral Syndrome and Oral, Cutaneous, Renal, Ocular, Metabolic, and Cardiac Diseases)

Stephen J. Chapman, DM
Consultant in Respiratory Medicine, Department of Respiratory Medicine, Oxford University Hospitals, Oxford, United Kingdom
Human Genetics and Infection

Catherine A. Chappell, MD, MSc
Assistant Professor, Department of Obstetrics, Gynecology and Reproductive Sciences, University of Pittsburgh, Pittsburgh, Pennsylvania
Human Immunodeficiency Virus Infection in Women

James D. Chappell, MD, PhD
Research Associate Professor of Pediatrics, Vanderbilt University School of Medicine, Nashville, Tennessee
Biology of Viruses and Viral Diseases

Lea Ann Chen, MD
Assistant Professor, Division of Gastroenterology, New York University Langone School of Medicine, New York, New York
Prebiotics, Probiotics, and Synbiotics

Sharon C-A. Chen, PhD, MB BS
Infectious Diseases Physician and Medical Microbiologist, Centre for Infectious Diseases and Microbiology, Westmead Hospital, Westmead; Director of Microbiology, Institute of Clinical Pathology and Medical Research, New South Wales Health Pathology, Westmead; Clinical Associate Professor, Sydney Medical School, University of Sydney, Sydney, New South Wales, Australia
Nocardia *Species*

Dr. Augusto Dulanto Chiang
Staff Clinician, Bacterial Pathogenesis and Resistance Unit, Laboratory of Clinical Immunology and Microbiology, National Institute of Allergy and Infectious Diseases, Bethesda, Maryland
Pasteurella Species

Sanjiv Chopra, MBBS
Professor of Medicine, Harvard Medical School, Boston, Massachusetts
Hepatitis E Virus

Anthony W. Chow, MD
Professor Emeritus, Internal Medicine/Infectious Diseases, University of British Columbia; Honorary Consultant, Internal Medicine/Infectious Diseases, Vancouver Hospital, Vancouver, British Columbia, Canada
Infections of the Oral Cavity, Neck, and Head

Cornelius J. Clancy, MD
Associate Professor of Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania
Antifungal Drugs: Echinocandins

Richard B. Clark, PhD, D(ABMM)
Infectious Disease Department, Quest Diagnostics & Nichols Institute, Chantilly, Virginia
Capnocytophaga

Jeffrey I. Cohen, MD
Chief, Laboratory of Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland
Herpes B Virus
Human Herpesvirus Types 6 and 7 (Exanthem Subitum)
Introduction to Herpesviridae

Myron S. Cohen, MD
Yergin-Bates Eminent Professor of Medicine, Microbiology and Epidemiology; Director, Institute of Global Health and Infectious Diseases, The University of North Carolina at Chapel Hill, Chapel Hill, North Carolina
The Acutely Ill Patient With Fever and Rash

Yehuda Z. Cohen, MD
Director, Translational Medicine and Clinical Pharmacology, Sanofi, Bridgewater, New Jersey
The Common Cold

Ronit Cohen-Poradosu, MD
Senior Physician, Infectious Diseases Unit, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel
Anaerobic Infections: General Concepts

Susan E. Cohn, MD, MPH
Professor of Medicine, Northwestern University Feinberg School of Medicine, Chicago, Illinois
Human Immunodeficiency Virus Infection in Women

Benjamin Colton, PharmD
Infectious Diseases Clinical Pharmacist, Department of Pharmacy, National Institutes of Health, Bethesda, Maryland
Antifungal Drugs: Flucytosine

Mark Connors, MD
Chief, HIV-Specific Immunity Section, Laboratory of Immunoregulation, National Institute of Allergy and Infectious Disease, National Institutes of Health, Bethesda, Maryland
The Immunology of Human Immunodeficiency Virus Infection

Nathanial K. Copeland, MD, MTM&H
Director, Kombewa Clinical Research Center, United States Army Medical Research Directorate—Africa, Kombewa, Kenya; Assistant Professor, Department of Medicine, Uniformed Services University of the Health Sciences, Bethesda, Maryland
Leishmania *Species: Visceral (Kala-Azar), Cutaneous, and Mucosal Leishmaniasis*

Lawrence Corey, MD
Past President and Director, Member, Fred Hutchinson Cancer Research Center; Professor of Medicine and Laboratory Medicine, University of Washington, Seattle, Washington
Herpes Simplex Virus

Sara E. Cosgrove, MD, MS
Professor of Medicine, Division of Infectious Diseases, Johns Hopkins University School of Medicine, Baltimore, Maryland
Antimicrobial Stewardship

Mackenzie L. Cottrell, PharmD
Research Assistant Professor, Division of Pharmacotherapy and Experimental Therapeutics, Eshelman School of Pharmacy, University of North Carolina, Chapel Hill, North Carolina
Pharmacokinetics and Pharmacodynamics of Antiinfective Agents

Timothy L. Cover, MD
Professor of Medicine, Professor of Pathology, Microbiology, and Immunology, Vanderbilt University Medical Center; Veterans Affairs Tennessee Valley Healthcare System, Nashville, Tennessee
Helicobacter pylori *and Other Gastric* Helicobacter *Species*

Heather L. Cox, PharmD
Assistant Professor of Medicine and Infectious Diseases, Department of Medicine, University of Virginia School of Medicine; Clinical Coordinator, Infectious Diseases, Department of Pharmacy Services, University of Virginia Health System, Charlottesville, Virginia
Linezolid, Tedizolid, and Other Oxazolidinones

Ryan L. Crass, PharmD
Clinical Pharmacy Translational Science Fellow, Department of Clinical Pharmacy, College of Pharmacy, University of Michigan, Ann Arbor, Michigan
Tables of Antiinfective Agent Pharmacology

Cheston B. Cunha, MD
Medical Director, Antimicrobial Stewardship Program, Rhode Island Hospital and Miriam Hospital; Infectious Disease Division, Alpert School of Medicine, Brown University, Providence, Rhode Island
Viridans Streptococci, Nutritionally Variant Streptococci, and Groups C and G Streptococci

James W. Curran, MD, MPH
Dean and Professor of Epidemiology, Rollins School of Public Health, Emory University; Co-Director, Emory Center for AIDS Research, Atlanta, Georgia
Epidemiology and Prevention of AIDS and HIV Infection, Including Preexposure Prophylaxis and HIV Vaccine Development

Bart J. Currie, MBBS, DTM+H
Professor in Medicine, Department of Infectious Diseases, Royal Darwin Hospital, Global and Tropical Health Division, Menzies School of Health Research, Darwin, Australia
Burkholderia pseudomallei *and* Burkholderia mallei*: Melioidosis and Glanders*

Erika D'Agata, MD, MPH
Professor of Medicine, Department of Medicine, Brown University, Providence, Rhode Island
Pseudomonas aeruginosa *and Other* Pseudomonas *Species*

Jennifer S. Daly, MD
Professor, Departments of Medicine, Microbiology, and Physiological Systems, Division of Infectious Diseases, University of Massachusetts Medical School, Worcester, Massachusetts
Acute Pneumonia

Inger K. Damon, MD, PhD
Director, Division of High Consequence Pathogens and Pathology, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia
Orthopoxviruses: Vaccinia (Smallpox Vaccine), Variola (Smallpox), Monkeypox, and Cowpox
Other Poxviruses That Infect Humans: Parapoxviruses (Including Orf Virus), Molluscum Contagiosum, and Yatapoxviruses

Rabih O. Darouiche, MD
VA Distinguished Service Professor, Medicine, Surgery, and Physical Medicine and Rehabilitation, Michael E. DeBakey VAMC and Baylor College of Medicine, Houston, Texas
Infections in Patients With Spinal Cord Injury

Suzanne Dawid, MD, PhD
Andrew B. Briskin Associate Research Professor of Pediatrics, Associate Professor, Microbiology and Immunology, University of Michigan, Ann Arbor, Michigan
Infections in Asplenic Patients

George S. Deepe, Jr., MD
Professor, Internal Medicine/Infectious Diseases, University of Cincinnati College of Medicine, Cincinnati, Ohio
Histoplasma capsulatum *(Histoplasmosis)*

John P. Dekker, MD, PhD
Chief, Bacterial Pathogenesis and Antimicrobial Resistance Unit, Laboratory of Clinical Immunology and Microbiology, National Institute of Allergy and Infectious Diseases; Director, Genomics Section, Microbiology Service, Department of Laboratory Medicine, National Institutes of Health Clinical Center, Bethesda, Maryland
Classification of Streptococci

Carlos del Rio, MD
Professor and Chair, Hubert Department of Global Health, Rollins School of Public Health, Emory University; Co-Director, Emory Center for AIDS Research, Atlanta, Georgia
Epidemiology and Prevention of AIDS and HIV Infection, Including Preexposure Prophylaxis and HIV Vaccine Development

Frank R. DeLeo, PhD
Chief, Laboratory of Bacteriology, Rocky Mountain Laboratories, National Institute of Allergy and Infectious Diseases, Hamilton, Montana
Granulocytic Phagocytes

Gregory P. DeMuri, MD
Professor, University of Wisconsin School of Medicine and Public Health; Attending Physician, American Family Children's Hospital, Madison, Wisconsin
Sinusitis

Terence S. Dermody, MD
Professor and Chair, Department of Pediatrics, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania
Biology of Viruses and Viral Diseases

Robin Dewar, PhD
Clinical Monitoring Research Program Directorate, Frederick National Laboratory for Cancer Research sponsored by the National Cancer Institute, Frederick, Maryland
Diagnosis of Human Immunodeficiency Virus Infection

James H. Diaz, MD, MPHTM, DrPH
Professor of Public Health and Preventive Medicine, School of Public Health, Louisiana State University Health Sciences Center, New Orleans, Louisiana
Introduction to Ectoparasitic Diseases
Lice (Pediculosis)
Scabies
Myiasis and Tungiasis
Mites, Including Chiggers
Ticks, Including Tick Paralysis

Carl W. Dieffenbach, PhD
Director, Division of AIDS, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland
Innate (General or Nonspecific) Host Defense Mechanisms

Jules L. Dienstag, MD
Carl W. Walter Professor of Medicine, Harvard Medical School; Physician, Massachusetts General Hospital, Boston, Massachusetts
Viral Hepatitis
Antiviral Drugs Against Hepatitis Viruses

Yohei Doi, MD, PhD
Associate Professor of Medicine, Division of Infectious Diseases, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania
Ertapenem, Imipenem, Meropenem, Doripenem, and Aztreonam
Penicillins and β-Lactamase Inhibitors

Raphael Dolin, MD
Maxwell Finland Professor of Medicine (Microbiology and Molecular Genetics), Harvard Medical School; Attending Physician, Beth Israel Deaconess Medical Center; Brigham and Women's Hospital, Boston, Massachusetts
The Common Cold
Antiviral Agents: General Principles
Zoonotic Paramyxoviruses: Nipah, Hendra, and Menangle Viruses
Astroviruses and Picobirnaviruses
Noroviruses and Sapoviruses (Caliciviruses)
Rhinovirus
Miscellaneous Antiviral Agents (Interferons, Tecovirimat, Imiquimod, Pocapavir, Pleconaril)
California Encephalitis, Hantavirus Pulmonary Syndrome, Hantavirus Hemorrhagic Fever With Renal Syndrome, and Bunyavirus Hemorrhagic Fevers

Gerald R. Donowitz, MD
Professor of Medicine and Infectious Diseases/International Health, Department of Medicine, University of Virginia, Charlottesville, Virginia
Linezolid, Tedizolid, and Other Oxazolidinones

Curtis J. Donskey, MD
Professor of Medicine, Case Western Reserve School of Medicine; Staff Physician, Infectious Diseases Section, Cleveland VA Medical Center, Cleveland, Ohio
Clostridioides difficile (*Formerly* Clostridium difficile) *Infection*

Philip R. Dormitzer, MD, PhD
Vice President and Chief Scientific Officer Viral Vaccines, Pfizer, Pearl River, New York
Rotaviruses

J. Stephen Dumler, MD
Professor and Chair, Pathology, Uniformed Services University of the Health Sciences, Bethesda, Maryland
Rickettsia typhi *(Murine Typhus)*
Ehrlichia chaffeensis *(Human Monocytotropic Ehrlichiosis),* Anaplasma phagocytophilum *(Human Granulocytotropic Anaplasmosis), and Other Anaplasmataceae*

Kathryn Dupnik, MD
Assistant Professor, Medicine, Weill Cornell Medicine, New York, New York
Leprosy (Mycobacterium leprae)

Herbert L. DuPont, MD
Professor of Infectious Diseases, University of Texas School of Public Health and Mary W. Kelsey Chair, University of Texas McGovern Medical School, Houston, Texas
Bacillary Dysentery: Shigella *and Enteroinvasive* Escherichia coli

David T. Durack, MB, DPhil
Consulting Professor of Medicine, Duke University School of Medicine, Durham, North Carolina
Prevention of Infective Endocarditis

Marlene L. Durand, MD
Associate Professor of Medicine, Harvard Medical School; Physician, Division of Infectious Diseases, Massachusetts General Hospital; Director, Infectious Disease Service, Massachusetts Eye and Ear Infirmary, Boston, Massachusetts
Endophthalmitis
Introduction to Eye Infections
Periocular Infections
Infectious Causes of Uveitis

Xavier Duval, MD, PhD
Professor of Medicine, University of Paris-Diderot School of Medicine, Paris, France
Prevention of Infective Endocarditis

Paul H. Edelstein, MD
Professor of Pathology and Laboratory Medicine, University of Pennsylvania Perelman School of Medicine; Pathology and Laboratory Medicine, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania
Legionnaires' Disease and Pontiac Fever

John E. Edwards, Jr., MD
Professor of Medicine Emeritus, David Geffen School of Medicine at UCLA, Division of Infectious Diseases, Harbor-UCLA Medical Center, Senior Investigator, Los Angeles Biomedical Institute at Harbor UCLA, Los Angeles, California
Candida *Species*

Morven S. Edwards, MD
Professor of Pediatrics, Baylor College of Medicine; Attending Physician, Department of Pediatrics, Section of Infectious Diseases, Texas Children's Hospital, Houston, Texas
Streptococcus agalactiae *(Group B Streptococci)*

Richard T. Ellison III, MD
Professor, Departments of Medicine, Microbiology, and Physiological Systems, Division of Infectious Diseases, University of Massachusetts Medical School, Worcester, Massachusetts
Acute Pneumonia

Alan C. Embry, PhD
Chief, Respiratory Diseases Branch, Division of Microbiology and Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, US Department of Health and Human Services, Rockville, Maryland
Innate (General or Nonspecific) Host Defense Mechanisms

Timothy P. Endy, MD, MPH
Chair, Department of Microbiology and Immunology, Professor of Medicine, State University of New York (SUNY) Upstate Medical University, Syracuse, New York
Flaviviruses (Dengue, Yellow Fever, Japanese Encephalitis, West Nile Encephalitis, Usutu Encephalitis, St. Louis Encephalitis, Tick-Borne Encephalitis, Kyasanur Forest Disease, Alkhurma Hemorrhagic Fever, Zika)

N. Cary Engleberg, MD, DTM&H
Professor, Department of Internal Medicine, Infectious Disease Division, University of Michigan Medical School, Ann Arbor, Michigan
Chronic Fatigue Syndrome (Systemic Exertion Intolerance Disease)

Janet A. Englund, MD
Professor, Pediatrics, University of Washington/Seattle Children's Hospital, Seattle, Washington
Respiratory Syncytial Virus

Hakan Erdem, MD
Infectious Diseases International Research Initiative (ID-IRI) Lead Coordinator, Ankara, Turkey
*Brucellosis (*Brucella *Species)*

Peter B. Ernst, DVM, PhD
Professor of Pathology, Director, Comparative Pathology and Medicine, Chiba University-UC San Diego Center for Mucosal Immunity, Allergy and Vaccine Development, University of California San Diego School of Medicine, La Jolla, California
Mucosal Immunity

Rick M. Fairhurst, MD, PhD
Senior Safety Physician, Chief Medical Officer's Office, Oncology R&D, AstraZeneca, Gaithersburg, Maryland
Malaria (Plasmodium *Species*)

Jessica K. Fairley, MD, MPH
Associate Professor of Medicine and Global Health, Emory University School of Medicine, Atlanta, Georgia
Tapeworms (Cestodes)

Stanley Falkow, PhD†
Robert W. and Vivian K. Cahill Professor in Cancer Research, Emeritus, Stanford University School of Medicine, Stanford, California
A Molecular Perspective of Microbial Pathogenicity

Ann R. Falsey, MD
Professor of Medicine, Department of Medicine, Division of Infectious Diseases, University of Rochester School of Medicine, Rochester, New York
Human Metapneumovirus

Anthony S. Fauci, MD
Chief, Laboratory of Immunoregulation, Director, National Institute of Allergy and Infectious Disease, National Institutes of Health, Bethesda, Maryland
The Immunology of Human Immunodeficiency Virus Infection

Thomas Fekete, MD
Professor of Medicine, Chair of Medicine, Temple University School of Medicine, Philadelphia, Pennsylvania
Bacillus *Species and Related Genera Other Than* Bacillus anthracis

Paul D. Fey, PhD
Professor, Department of Pathology and Microbiology, University of Nebraska Medical Center College of Medicine, Omaha, Nebraska
Staphylococcus epidermidis *and Other Coagulase-Negative Staphylococci*

†Deceased.

Steven M. Fine, MD, PhD
Associate Professor of Medicine, Division of Infectious Diseases, University of Rochester Medical Center, Rochester, New York
Vesicular Stomatitis Virus and Related Vesiculoviruses (Chandipura Virus)

Daniel W. Fitzgerald, MD
Professor of Medicine, Microbiology, and Immunology, Weill Cornell Medical College, New York, New York
Mycobacterium tuberculosis

Anthony R. Flores, MD, MPH, PhD
Associate Professor, Pediatrics, Infectious Diseases, UTHSC/McGovern Medical School, Houston, Texas
Pharyngitis

Pierre-Edouard Fournier, MD, PhD
IHU Meditérranée-Infection, Aix-Marseille University, Marseille, France
Rickettsia akari *(Rickettsialpox)*

Vance G. Fowler, Jr., MD, MHS
Professor, Departments of Medicine and Molecular Genetics and Microbiology, Duke University Medical Center, Durham, North Carolina
Endocarditis and Intravascular Infections

David O. Freedman, MD
Professor Emeritus, Infectious Diseases, University of Alabama at Birmingham; Medical Director, Shoreland Travax, Birmingham, Alabama
Infections in Returning Travelers
Protection of Travelers

Arthur M. Friedlander, MD
Adjunct Professor of Medicine, School of Medicine, Uniformed Services University of the Health Sciences, Bethesda, Maryland; Senior Scientist, U.S. Army Medical Research Institute of Infectious Diseases, Frederick, Maryland
Bacillus anthracis *(Anthrax)*

John N. Galgiani, MD
Professor of Internal Medicine, Director, Valley Fever Center for Excellence, University of Arizona College of Medicine, Tucson, Arizona
Coccidioidomycosis (Coccidioides *Species*)

John I. Gallin, MD
NIH Associate Director for Clinical Research and Chief Scientific Officer of the NIH Clinical Center, National Institutes of Health, Bethesda, Maryland
Evaluation of the Patient With Suspected Immunodeficiency

Robert C. Gallo, MD
Director, Institute of Human Virology, Homer and Martha Gudelsky Distinguished Professor in Medicine, University of Maryland School of Medicine, Baltimore, Maryland
Human Immunodeficiency Viruses

Monica Gandhi, MD, MPH
Professor of Medicine, University of California, San Francisco (UCSF), San Francisco, California
Human Immunodeficiency Virus Infection in Women

Wendy S. Garrett, MD, PhD
Assistant Professor, Immunology and Infectious Diseases & Genetic and Complex Diseases, Department of Medicine, Harvard School of Public Health, Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, Massachusetts
Diseases Caused by Clostridium
Bacteroides, Prevotella, Porphyromonas, *and* Fusobacterium *Species (and Other Medically Important Anaerobic Gram-Negative Bacilli)*

Gregory M. Gauthier, MD
Associate Professor (CHS), Department of Medicine, University of Wisconsin-Madison, Madison, Wisconsin
Blastomycosis

Charlotte A. Gaydos, DrPH, MPH, MS
Professor of Medicine, Division of Infectious Diseases, Johns Hopkins University School of Medicine; Emergency Medicine Department and Epidemiology, Population, Family and Reproductive Health, Bloomberg Johns Hopkins School of Public Health; Director, International Sexually Transmitted Diseases Research Laboratory, Baltimore, Maryland
Chlamydia pneumoniae

Juan C. Gea-Banacloche, MD
Senior Associate Consultant, Infectious Disease, Mayo Clinic AZ, Phoenix, Arizona
Brain Abscess

Thomas W. Geisbert, PhD
Professor, Department of Microbiology and Immunology, The University of Texas Medical Branch, Galveston, Texas
Marburg and Ebola Virus Hemorrhagic Fevers

Jeffrey A. Gelfand, MD
Clinical Professor of Medicine, Harvard Medical School; Attending Physician, Infectious Diseases Division, Massachusetts General Hospital, Boston, Massachusetts
Babesia *Species*

Steven P. Gelone, PharmD
President and Chief Operating Officer, Nabriva Therapeutics, King of Prussia, Pennsylvania
Topical Antibacterials

Dale N. Gerding, MD
Professor of Medicine, Loyola University Chicago Stritch School of Medicine, Maywood, Illinois; Research Physician, Department of Medicine, Edward Hines Jr. VA Hospital, Hines, Illinois
Clostridioides difficile (*Formerly* Clostridium difficile) *Infection*

Anne A. Gershon, MD
Professor of Pediatrics, Columbia University Vagelos College of Physicians and Surgeons, New York, New York
Rubella Virus (German Measles)
Measles Virus (Rubeola)

Janet R. Gilsdorf, MD
Robert P. Kelch Research Professor Emerita of Pediatrics, University of Michigan Medical School and C.S. Mott Children's Hospital, Ann Arbor, Michigan
Infections in Asplenic Patients

Pushpanjali Giri, BA
Research Specialist, Department of Ophthalmology, University of Illinois at Chicago, Chicago, Illinois
Microbial Keratitis

Howard S. Gold, MD
Medical Director of Antimicrobial Stewardship, Silverman Institute for Health Care Quality and Safety; Division of Infectious Diseases, Beth Israel Deaconess Medical Center, Boston, Massachusetts
Outpatient Parenteral Antimicrobial Therapy

Ellie J.C. Goldstein, MD
Director, R.M. Alden Research Laboratory, Clinical Professor of Medicine, UCLA School of Medicine, Santa Monica, California
Bites

Ángel González-Marín, PhD
Professor, School of Microbiology, Universidad de Antioquia, Medellin, Antioquia, Colombia
Paracoccidioidomycosis

Paul S. Graman, MD
Professor of Medicine, University of Rochester School of Medicine and Dentistry; Attending Physician, Infectious Diseases Division, Strong Memorial Hospital, Rochester, New York
Esophagitis

M. Lindsay Grayson, MD
Infectious Diseases and Microbiology Departments, Austin Health, Department of Epidemiology and Preventive Medicine, Monash University; Department of Medicine, University of Melbourne, Melbourne, Australia
Fusidic Acid

David Greenberg, MD
Associate Professor, Internal Medicine and Microbiology, University of Texas Southwestern, Dallas, Texas
Stenotrophomonas maltophilia *and* Burkholderia cepacia *Complex*

Matthew H. Greene, MD
Assistant Professor, Infectious Diseases, Vanderbilt University Medical Center, Nashville, Tennessee
Enterobacteriaceae

Patricia M. Griffin, MD
Chief, Enteric Diseases Epidemiology Branch, Division of Foodborne, Bacterial, and Mycotic Diseases, National Center for Zoonotic, Vectorborne, and Enteric Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia
Foodborne Disease

David E. Griffith, MD
Professor of Medicine and William A. and Elizabeth B. Moncrief Distinguished Professor, Section Chief, Pulmonary Infectious Disease, University of Texas Health Science Center at Tyler, Tyler, Texas; Medical Liaison, Texas Center for Infectious Disease; Assistant Medical Director, Heartland National Tuberculosis Center, San Antonio, Texas
Antimycobacterial Agents

Richard L. Guerrant, MD
Thomas H. Hunter Professor of International Medicine, Founding Director, Center for Global Health, Division of Infectious Diseases and International Health, University of Virginia School of Medicine, Charlottesville, Virginia
Diarrhea With Little or No Fever
Acute Dysentery Syndromes (Diarrhea With Fever)

Hanefi C. Gul, MD
Department of Infectious Diseases and Clinical Microbiology, Gulhane Training and Research Hospital, Ankara, Turkey
*Brucellosis (*Brucella *Species)*

David A. Haake, MD
Professor, Departments of Medicine, Urology, and Microbiology, Immunology, and Molecular Genetics, The David Geffen School of Medicine at UCLA; Staff Physician, Department of Medicine, Division of Infectious Diseases, The Veterans Affairs Greater Los Angeles Healthcare System, Los Angeles, California
Leptospira *Species (Leptospirosis)*

David W. Haas, MD
Professor of Medicine, Pharmacology, Pathology, Microbiology, and Immunology, Vanderbilt University School of Medicine, Nashville, Tennessee
Mycobacterium tuberculosis

Ghady Haidar, MD
Assistant Professor of Medicine, Department of Medicine, Division of Infectious Diseases, University of Pittsburgh and UPMC, Pittsburgh, Pennsylvania
Infections in Solid-Organ Transplant Recipients

Joelle Hallak, MS, PhD
Assistant Professor, Executive Director, Ophthalmic Clinical Trials and Translational Center, Department of Ophthalmology and Visual Sciences, University of Illinois at Chicago, Chicago, Illinois
Microbial Keratitis

Scott A. Halperin, MD
Professor, Departments of Pediatrics and Microbiology & Immunology, Director, Canadian Center for Vaccinology, Dalhousie University, Halifax, Canada
Bordetella pertussis

Margaret R. Hammerschlag, MD
Professor of Pediatrics and Medicine, State University of New York Downstate College of Medicine; Director, Pediatric Infectious Disease Fellowship Training Program, State University of New York Downstate Medical Center, Brooklyn, New York
Chlamydia pneumoniae

Rashidul Haque, MD
Scientist and Head of Parasitology Laboratory, Laboratory Sciences Division, International Centre for Diarrhoeal Disease Research, Bangladesh, Dhaka, Bangladesh
Entamoeba *Species, Including Amebic Colitis and Liver Abscess*

Jason B. Harris, MD, MPH
Associate Professor of Pediatrics, Harvard Medical School; Chief, Pediatric Global Health, Massachusetts General Hospital, Boston, Massachusetts
Syndromes of Enteric Infection
Typhoid Fever, Paratyphoid Fever, and Typhoidal Fevers

Joshua D. Hartzell, MD, MS-HPed
Assistant Dean for Faculty Development, Department of Medicine, Uniformed Services University, Bethesda, Maryland
Coxiella burnetii *(Q Fever)*

Rodrigo Hasbun, MD, MPH
Professor, Section of Infectious Diseases, McGovern Medical School-UT Health, Houston, Texas
Approach to the Patient With Central Nervous System Infection
Acute Meningitis

Claudia Hawkins, MD, MPH
Associate Professor, Department of Infectious Diseases, Northwestern University Feinberg School of Medicine, Chicago, Illinois
Hepatitis B Virus
Hepatitis Delta Virus

Roderick J. Hay, DM
Emeritus Professor of Cutaneous Infection, Department of Dermatology, Kings College London, London, United Kingdom
Dermatophytosis (Ringworm) and Other Superficial Mycoses

David K. Henderson, MD
Deputy Director for Clinical Care, Clinical Center, National Institutes of Health, Bethesda, Maryland
Infections Caused by Percutaneous Intravascular Devices

Kevin P. High, MD, MS
Professor of Medicine and Translational Science, Internal Medicine, Wake Forest School of Medicine; President, Wake Forest Baptist Health, Winston-Salem, North Carolina
Infections in Older Adults

Adrian V.S. Hill, DPhil, DM
Professor of Human Genetics, Wellcome Centre for Human Genetics, University of Oxford, Oxford, United Kingdom
Human Genetics and Infection

Alan R. Hinman, MD, MPH
The Task Force for Global Health, Center for Vaccine Equity, Decatur, Georgia
Immunization

Martin S. Hirsch, MD
Professor of Medicine, Harvard Medical School; Professor of Infectious Diseases and Immunology, Harvard School of Public Health; Senior Physician, Infectious Diseases Service, Massachusetts General Hospital, Boston, Massachusetts
Antiretroviral Therapy for Human Immunodeficiency Virus Infection

Sarah Hochman, MD
Associate Hospital Epidemiologist, Infection Prevention and Control, NYU Langone Health; Assistant Professor, Department of Medicine, Division of Infectious Diseases and Immunology, NYU School of Medicine, New York, New York
Acinetobacter *Species*

Bruno Hoen, MD, PhD
Professor of Medicine, University of Lorraine School of Medicine, Nancy, France
Prevention of Infective Endocarditis

Tobias M. Hohl, MD, PhD
Chief, Infectious Disease Service, Associate Member, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, New York
Cell-Mediated Defense Against Infection

Steven M. Holland, MD
Director, Intramural Research, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland
Evaluation of the Patient With Suspected Immunodeficiency

Thomas L. Holland, MD
Assistant Professor of Medicine, Division of Infectious Diseases, Duke University Medical Center, Durham, North Carolina
Endocarditis and Intravascular Infections

Robert S. Holzman, MD
Professor Emeritus of Medicine, Department of Medicine, New York University School of Medicine, New York, New York
Mycoplasma pneumoniae *and Atypical Pneumonia*

David C. Hooper, MD
Associate Chief, Division of Infectious Diseases, Massachusetts General Hospital; Chief, Infection Control Unit, Massachusetts General Hospital, Boston, Massachusetts
Quinolones

Thomas M. Hooton, MD
Professor of Clinical Medicine, Department of Medicine, Clinical Director, Division of Infectious Diseases, University of Miami Miller School of Medicine; Chief of Medicine, Miami VA Health System, Miami, Florida
Health Care–Associated Urinary Tract Infections

Susan E. Hoover, MD, PhD
Associate Professor, Division of Infectious Disease, Sanford School of Medicine, Sioux Falls, South Dakota
Chronic Meningitis

Harold W. Horowitz, MD
Professor of Clinical Medicine, Weill Cornell School of Medicine, New York, New York; Chief of Service, Infectious Diseases, New-York Presbyterian Brooklyn Methodist Hospital, Brooklyn, New York
Acute Exacerbations of Chronic Obstructive Pulmonary Disease

James M. Horton, MD
Division of Infectious Diseases, Department of Internal Medicine, Carolinas Medical Center, Charlotte, North Carolina
Urinary Tract Agents: Nitrofurantoin, Fosfomycin, and Methenamine
Relapsing Fever Caused by Borrelia *Species*

Duane R. Hospenthal, MD, PhD
Adjunct Professor of Medicine, Department of Medicine, Infectious Disease Division, University of Texas Health Science Center at San Antonio; Partner, San Antonio Infectious Diseases Consultants, San Antonio, Texas
Agents of Chromoblastomycosis
Agents of Mycetoma
Uncommon Fungi and Related Species

Peter J. Hotez, MD, PhD
Dean, National School of Tropical Medicine; Professor, Pediatrics and Molecular & Virology and Microbiology; Head, Section of Pediatric Tropical Medicine, Baylor College of Medicine, Texas Children's Hospital Endowed Chair of Tropical Pediatrics; Director, Sabin Vaccine Institute, Texas Children's Hospital Center for Vaccine Development; University Professor, Department of Biology, Baylor University; President, Sabin Vaccine Institute, Baker Institute, Fellow in Disease and Poverty, Rice University; Co-Editor-in-Chief, PLoS Neglected Tropical Diseases, Houston, Texas
Intestinal Nematodes (Roundworms)

Noreen A. Hynes, MD, MPH, DTM&H
Associate Professor of Medicine (Infectious Diseases), School of Medicine and International Health (Global Epidemiology and Control), Bloomberg School of Public Health, Johns Hopkins University; Associate Medical Director, Biocontainment Unit (BCU), Johns Hopkins Hospital, Baltimore, Maryland
Bioterrorism: An Overview

Nicole M. Iovine, MD, PhD
Associate Professor of Medicine, University of Florida; Hospital Epidemiologist, UF Health, Gainesville, Florida
Campylobacter jejuni *and Related Species*

Michael G. Ison, MD, MS
Professor of Medicine and Surgery, Northwestern University Feinberg School of Medicine, Chicago, Illinois
Parainfluenza Viruses

Preeti Jaggi, MD
Department of Pediatrics, Division of Infectious Diseases, Emory University; Children's Healthcare of Atlanta, Atlanta, Georgia
Nonsuppurative Poststreptococcal Sequelae: Rheumatic Fever and Glomerulonephritis

J. Michael Janda, PhD, D(ABMM)
Laboratory Director, Public Health Laboratory, Department of Public Health, County of Los Angeles, Downey, California
Capnocytophaga

Edward N. Janoff, MD
Professor of Medicine, Immunology, and Microbiology, Infectious Diseases, University of Colorado Denver; Director, Mucosal and Vaccine Research Center (MAVRC), Rocky Mountain Regional Veterans Affairs Medical Center, Aurora, Colorado
Streptococcus pneumoniae

Daniel Jernigan, MD
Director, Influenza Division, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia
Emerging and Reemerging Infectious Disease Threats

Eric C. Johannsen, MD
Associate Professor, Departments of Medicine and Oncology, University of Wisconsin-Madison; Attending Physician, Division of Infectious Diseases, University of Wisconsin Hospitals and Clinics, Madison, Wisconsin
Epstein-Barr Virus (Infectious Mononucleosis, Epstein-Barr Virus—Associated Malignant Disease, and Other Diseases)

Jennie E. Johnson, MD
Assistant Professor, Division of Infectious Disease, Alpert Medical School, Brown University, Providence, Rhode Island
Listeria monocytogenes

Jonathan J. Juliano, MD, MSPH
Associate Professor, Medicine, University of North Carolina, Chapel Hill, North Carolina
The Acutely Ill Patient With Fever and Rash

Mini Kamboj, MD
Chief Medical Epidemiologist, Associate Member, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, New York
Health Care–Acquired Hepatitis

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
Anaerobic Infections: General Concepts

Donald Kaye, MD
Professor of Medicine, Drexel University College of Medicine, Philadelphia, Pennsylvania
Polymyxins (Polymyxin B and Colistin)

Keith S. Kaye, MD, MPH
Professor of Medicine, University of Michigan Medical School, Ann Arbor, Michigan
Polymyxins (Polymyxin B and Colistin)

Kenneth M. Kaye, MD
Associate Professor, Department of Medicine, Harvard Medical School, Attending Physician, Division of Infectious Diseases, Brigham and Women's Hospital, Boston, Massachusetts
Epstein-Barr Virus (Infectious Mononucleosis, Epstein-Barr Virus–Associated Malignant Disease, and Other Diseases)
Kaposi–Sarcoma-Associated Herpesvirus (Human Herpesvirus 8)

James W. Kazura, MD
Professor of International Health, Center for Global Health and Diseases, Case Western Reserve University School of Medicine, Cleveland, Ohio
Tissue Nematodes, Including Trichinellosis, Dracunculiasis, Filariasis, Loiasis, and Onchocerciasis

Jay S. Keystone, MD, MSc (CTM)
Professor of Medicine, University of Toronto; Senior Staff Physician, Tropical Disease Unit, Toronto General Hospital, Toronto, Ontario, Canada
Cyclospora cayetanensis, Cystoisospora belli, Sarcocystis *Species*, Balantidium coli, *and* Blastocystis *Species*

Rima F. Khabbaz, MD
Director, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia
Emerging and Reemerging Infectious Disease Threats

David A. Khan, MD
Professor of Medicine and Pediatrics, Internal Medicine, University of Texas Southwestern Medical Center, Dallas, Texas
Antibiotic Allergy

Yury Khudyakov, PhD
Chief, Molecular Epidemiology and Bioinformatics Laboratory, Division of Viral Hepatitis, Centers for Disease Control and Prevention; Chief, Molecular Epidemiology and Bioinformatics Laboratory, Atlanta, Georgia
Hepatitis A Virus

Rose Kim, MD
Assistant Dean for Faculty Affairs, Associate Professor of Medicine, Department of Medicine, Cooper Medical School of Rowan University, Camden, New Jersey
Other Coryneform Bacteria, Arcanobacterium haemolyticum, *and Rhodococci*

Charles H. King, MD, MS
Professor Emeritus of International Health, Center for Global Health and Diseases, Case Western Reserve University, Cleveland, Ohio
Tapeworms (Cestodes)

Louis V. Kirchhoff, MD, MPH
Professor of Internal Medicine, University of Iowa; Staff Physician, Medical Service, Department of Veterans Affairs Medical Center, Iowa City, Iowa
Agents of African Trypanosomiasis (Sleeping Sickness)
Drugs for Protozoal Infections Other Than Malaria
Trypanosoma *Species (American Trypanosomiasis, Chagas Disease): Biology of Trypanosomes*

Beth D. Kirkpatrick, MD
Professor and Chair, Microbiology and Molecular Genetics, University of Vermont College of Medicine, Burlington, Vermont
Campylobacter jejuni *and Related Species*

Hiroshi Kiyono, DDS, PhD
Distinguished Professor, Division of Mucosal Immunology, IMSUT Distinguished Professor Unit, International Research and Development Center for Mucosal Vaccines, The Institute of Medical Science, The University of Tokyo, Tokyo, Japan; Professor, Mucosal Immunology and Allergy Therapeutics Institute for Global Prominent Research, Graduate School of Medicine, Chiba University; Professor of Medicine, Division of Gastroenterology, Department of Medicine, School of Medicine, CU-UCSD Center for Mucosal Immunology, Allergy and Vaccines, University of California San Diego, La Jolla, California
Mucosal Immunity

Bruce S. Klein, MD
Gerard B. Odell and Shirley S. Matchette Professor, Pediatrics, Professor, Internal Medicine, Medical Microbiology and Immunology, University of Wisconsin-Madison, Madison, Wisconsin
Blastomycosis

Michael Klompas, MD, MPH
Professor of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute; Hospital Epidemiologist, Brigham and Women's Hospital, Boston, Massachusetts
Nosocomial Pneumonia

Bettina M. Knoll, MD, PhD
Associate Professor of Medicine, New York Medical College, Transplant Infectious Diseases, Westchester Medical Center, Valhalla, New York
Prosthetic Valve Endocarditis

Kirk U. Knowlton, MD
Director of Cardiovascular Research, Intermountain Heart Institute Intermountain Medical Center, Salt Lake City, Utah; Adjunct Professor of Medicine, University of Utah, Salt Lake City, Utah; Professor Emeritus, University of California San Diego, La Jolla, California
Myocarditis and Pericarditis

Jane E. Koehler, MA, MD
Professor of Medicine, Division of Infectious Diseases, Microbial Pathogenesis and Host Defense Program, Department of Medicine, University of California at San Francisco, San Francisco, California
Bartonella, *Including Cat-Scratch Disease*

Stephan A. Kohlhoff, MD
Associate Professor of Pediatrics and Medicine, State University of New York Downstate College of Medicine; Director, Division of Pediatric Infectious Diseases, State University of New York Downstate Medical Center, Brooklyn, New York
Chlamydia pneumoniae

Eija Könönen, DDS, PhD
Professor, Institute of Dentistry, University of Turku, Turku, Finland
Anaerobic Cocci and Anaerobic Gram-Positive Nonsporulating Bacilli

Dimitrios P. Kontoyiannis, MD
Frances King Black Endowed Professor, Department of Infectious Diseases, Division of Internal Medicine; Deputy Head, Division of Internal Medicine, The University of Texas MD Anderson Cancer Center, Houston, Texas
Agents of Mucormycosis and Entomophthoramycosis

Igor J. Koralnik, MD
Jean Schweppe Armour Professor of Neurology and Medicine Chair, Department of Neurological Sciences; Section Chief, Neuroinfectious Diseases Director, Neuroimmunology Fellowship, Rush University Medical Center, Chicago, Illinois
JC, BK, and Other Polyomaviruses: Progressive Multifocal Leukoencephalopathy (PML)
Neurologic Diseases Caused by Human Immunodeficiency Virus Type 1 and Opportunistic Infections

Poonum S. Korpe, MD
Assistant Scientist, Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland
Introduction to Protozoal Diseases

Anita A. Koshy, MD
Associate Professor, Departments of Neurology and Immunobiology, The University of Arizona, Tucson, Arizona
Free-Living Amebae

Joseph A. Kovacs, MD
Senior Investigator, Head, AIDS Section, Critical Care Medicine Department, National Institute of Health Clinical Center, Bethesda, Maryland
Toxoplasma gondii

Andrew T. Kroger, MD, MPH
Medical Officer, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia
Immunization

Matthew J. Kuehnert, MD
Medical Director, MTF Biologics, Edison, New Jersey; Hackensack Meridian School of Medicine at Seton Hall, Nutley, New Jersey
Transfusion- and Transplantation-Transmitted Infections

Nalin M. Kumar, Dphil
Professor of Ophthalmology,
Department of Ophthalmology and Visual Sciences, University of Illinois at Chicago, Chicago, Illinois
Microbial Conjunctivitis

Merin Elizabeth Kuruvilla, MD
Division of Allergy/Immunology, Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, Texas
Antibiotic Allergy

Regina C. LaRocque, MD, MPH
Assistant Professor of Medicine, Harvard Medical School, Division of Infectious Diseases, Massachusetts General Hospital, Boston, Massachusetts
Syndromes of Enteric Infection

Mary T. LaSalvia, MD
Clinical Director, Division of Infectious Diseases, Beth Israel Deaconess Medical Center; Medical Director of Ambulatory Care Quality, Silverman Institute for Health Care Quality and Safety, Beth Israel Deaconess Medical Center, Boston, Massachusetts
Outpatient Parenteral Antimicrobial Therapy

Howard L. Leaf, MD
Assistant Professor of Medicine, Division of Infectious Diseases, New York University School of Medicine; Infectious Diseases Section, VA New York Harbor Healthcare System, New York, New York
Mycoplasma pneumoniae *and Atypical Pneumonia*

James E. Leggett, MD
Associate Professor of Medicine, Oregon Health & Science University; Infectious Diseases Consultant, Medical Education, Providence Portland Medical Center, Portland, Oregon
Aminoglycosides

Alexander J. Lepak, MD
Assistant Professor, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin
Cephalosporins

Paul N. Levett, PhD, DSc
British Columbia Centre for Disease Control, Public Health Laboratory, Vancouver, British Columbia, Canada
Leptospira *Species (Leptospirosis)*

Donald P. Levine, MD
Professor Emeritus, Department of Medicine, Wayne State University, Detroit, Michigan
Infections in Injection Drug Users

Matthew E. Levison, MD
Professor of Public Health, Drexel University School of Public Health; Adjunct Professor of Medicine, Drexel University College of Medicine, Philadelphia, Pennsylvania
Peritonitis and Intraperitoneal Abscesses

Alexandra Levitt, PhD
Health Scientist, Special Advisor for Strategic Information Assessment to the Deputy Director for Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia
Emerging and Reemerging Infectious Disease Threats

Russell E. Lewis, PharmD
Associate Professor, Clinic of Infectious Diseases, Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy
Agents of Mucormycosis and Entomophthoramycosis

W. Conrad Liles, MD, PhD
Associate Chair and Professor of Medicine, University of Washington School of Medicine, Seattle, Washington
Immunomodulators

Aldo A.M. Lima, MD, PhD
Professor, Institute of Biomedicine, Federal University of Ceara, Fortaleza, Ceará, Brazil
Acute Dysentery Syndromes (Diarrhea With Fever)

Ajit P. Limaye, MD
Professor, Division of Allergy and Infectious Diseases, Director, Solid Organ Transplant Infectious Diseases Program, University of Washington School of Medicine, Seattle, Washington
Infections in Solid-Organ Transplant Recipients

Michail S. Lionakis, MD
Chief, Fungal Pathogenesis Section, Laboratory of Clinical Immunology and Microbiology, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland
Candida *Species*
Cell-Mediated Defense Against Infection

W. Ian Lipkin, MD
Director, Center for Infection and Immunity, Mailman School of Public Health, Columbia University, New York, New York
Zoonoses

Nathan Litman, MD
Professor of Pediatrics, Albert Einstein College of Medicine; Vice Chair, Clinical Affairs, Department of Pediatrics, Children's Hospital at Montefiore, Bronx, New York
Mumps Virus

Ruth Ann Luna, PhD
Director of Medical Metagenomics, Texas Children's Microbiome Center, Department of Pathology and Immunology, Baylor College of Medicine, Department of Pathology, Texas Children's Hospital, Houston, Texas
The Human Microbiome of Local Body Sites and Their Unique Biology

Joseph D. Lutgring, MD
Assistant Professor of Medicine, Division of Infectious Diseases, Emory University School of Medicine, Atlanta, Georgia
Other Gram-Negative and Gram-Variable Bacilli

Conan MacDougall, PharmD, MAS
Professor of Clinical Pharmacy, Department of Clinical Pharmacy, University of California San Francisco School of Pharmacy, San Francisco, California
Antimicrobial Stewardship

Susan Maddocks, MBBS, PhD
Infectious Diseases Physician and Medical Microbiologist, Centre for Infectious Diseases and Microbiology, Westmead Hospital, Westmead; Institute of Clinical Pathology and Medical Research, New South Wales Health Pathology, Westmead; Clinical Senior Lecturer, Sydney Medical School, University of Sydney, Sydney, New South Wales, Australia
Nocardia *Species*

Lawrence C. Madoff, MD
Professor of Medicine, University of Massachusetts Medical School; Director, Division of Epidemiology and Immunization, Massachusetts Department of Public Health, University of Massachusetts Memorial Medical Center, Division of Infectious Disease and Immunology, Worcester, Massachusetts
Appendicitis
Splenic Abscess
Infections of the Liver and Biliary System (Liver Abscess, Cholangitis, Cholecystitis)
Diverticulitis and Neutropenic Enterocolitis

Alan J. Magill, MD†
Director, Global Health Program, Bill & Melinda Gates Foundation, Seattle, Washington
Leishmania *Species: Visceral (Kala-Azar), Cutaneous, and Mucosal Leishmaniasis*

James H. Maguire, MD, MPH
Professor of Medicine, Harvard Medical School; Senior Physician, Division of Infectious Disease, Brigham and Women's Hospital, Boston, Massachusetts
Introduction to Helminth Infections
Trematodes (Schistosomes and Liver, Intestinal, and Lung Flukes)

Frank Maldarelli, MD, PhD
Head, Clinical Retrovirology Section, HIV Drug Resistance Program, National Cancer Institute -Frederick, National Institutes of Health, Frederick, Maryland
Diagnosis of Human Immunodeficiency Virus Infection

Lewis Markoff, MD
Laboratory Chief (Retired), Laboratory of Vector-Borne Virus Diseases, Center for Biologics Evaluation and Research, US Food and Drug Administration, Bethesda, Maryland
Alphaviruses (Chikungunya, Eastern Equine Encephalitis)

Jeanne M. Marrazzo, MD, MPH
Professor of Medicine, Division of Infectious Diseases, University of Alabama at Birmingham, Birmingham, Alabama
Neisseria gonorrhoeae *(Gonorrhea)*

Thomas J. Marrie, MD
Dean Emeritus, Faculty of Medicine, Dalhousie University, Halifax, Nova Scotia, Canada
Coxiella burnetii *(Q Fever)*

Thomas Marth, MD
Chief, Division of Internal Medicine, St. Elisabeth Krankenhaus, Lahnstein, Germany
Whipple Disease

David H. Martin, MD
Harry E. Dascomb, M.D., Professor of Medicine Emeritus, Department of Internal Medicine, Professor of Microbiology, Immunology, and Parasitology Emeritus, Louisiana State University Health Sciences Center, New Orleans, Louisiana
Genital Mycoplasmas: Mycoplasma genitalium, Mycoplasma hominis, *and* Ureaplasma *Species*

Gregory J. Martin, MD
Chief, Infectious Diseases - Tropical Medicine, Office of Medical Services, United States Department of State, Washington, DC
Bacillus anthracis *(Anthrax)*

†Deceased.

Francisco M. Marty, MD
Associate Professor of Medicine, Department of Medicine, Harvard Medical School; Division of Infectious Diseases, Brigham and Women's Hospital, Boston, Massachusetts
Cystic Fibrosis

Melanie Jane Maslow, MD
Chief, Infectious Diseases, VA New York Harbor Healthcare System; Professor of Medicine, Department of Internal Medicine, New York University School of Medicine, New York, New York
Rifamycins

Henry Masur, MD
Chief, Critical Care Medicine Department, Clinical Center, National Institutes of Health, Bethesda, Maryland
Management of Opportunistic Infections Associated With Human Immunodeficiency Virus Infection

Alison Mawle, MD
Associate Director for Laboratory Science, Centers for Disease Control and Prevention, Atlanta, Georgia
Immunization

Kenneth H. Mayer, MD
Professor of Medicine, Harvard Medical School; Professor in Global Health and Population, Harvard T.C. Chan School of Public Health; Attending Physician, Beth Israel Deaconess Medical Center, Boston, Massachusetts
Sulfonamides and Trimethoprim; Trimethoprim-Sulfamethoxazole

James S. McCarthy, MD
Professor of Medicine, Department of Infectious Diseases Royal Brisbane and Womens Hospital; Senior Scientist, QIMR Berghofer Medical Research Institute, University of Queensland, Brisbane, Australia
Antimalarial Drugs
Drugs for Helminths
Drugs for Protozoal Infections Other Than Malaria

William McCormack, MD
Distinguished Teaching Professor of Medicine and of Obstetrics and Gynecology, Emeritus, Division of Infectious Diseases, Department of Medicine, SUNY Downstate Medical Center, Brooklyn, New York
Vulvovaginitis and Cervicitis

Catherine C. McGowan, MD
Associate Professor, Department of Medicine, Division of Infectious Diseases, Vanderbilt University School of Medicine, Nashville, Tennessee
Prostatitis, Epididymitis, and Orchitis

Kenneth McIntosh, MD
Professor of Pediatrics, Harvard Medical School; Adjunct Physician, Division of Infectious Diseases, Boston Children's Hospital, Boston, Massachusetts
Coronaviruses, Including Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS)

Paul S. Mead, MD, MPH
Chief, Bacterial Disease Branch, Division of Vector-Borne Diseases, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention, Fort Collins, Colorado
Plague (Yersinia pestis)

Rojelio Mejia, MD
Assistant Professor of Infectious Diseases and Pediatrics, National School of Tropical Medicine, Baylor College of Medicine, Houston, Texas
Intestinal Nematodes (Roundworms)

Vijayashree Mekala, MD
University of Texas Medical Branch, Sugar Land, Texas
Rat-Bite Fever: Streptobacillus moniliformis *and* Spirillum minus

Nancy Messonnier, MD
Director, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia
Emerging and Reemerging Infectious Disease Threats

Małgorzata Mikulska, MD
Division of Infectious Diseases, Department of Health Sciences (DISSAL), University of Genoa; IRCCS Ospedale Policlinico San Martino, Genoa, Italy
Prophylaxis and Empirical Therapy of Infection in Cancer Patients

Robert F. Miller, MB BS
Professor, Institute for Global Health, University College London, London, United Kingdom
Pneumocystis *Species*

Samuel I. Miller, MD
Professor of Medicine, Microbiology, and Genome Sciences, University of Washington School of Medicine, Seattle, Washington
Salmonella *Species*

William R. Miller, MD
Assistant Professor, Department of Internal Medicine, Division of Infectious Diseases, University of Texas Health Science Center at Houston, McGovern Medical School,
Houston, Texas
Enterococcus *Species,* Streptococcus gallolyticus *Group, and* Leuconostoc *Species*

Matthew Moffa, DO
Medical Director of Infection Prevention, West Penn Hospital, Division of Infectious Diseases, Allegheny Health Network, Pittsburgh, Pennsylvania
Tetracyclines, Glycylcyclines, and Chloramphenicol

Susan Moir, PhD
Chief, B-Cell Immunology Unit, Laboratory of Immunoregulation, National Institute of Allergy and Infectious Disease, National Institutes of Health, Bethesda, Maryland
The Immunology of Human Immunodeficiency Virus Infection

José G. Montoya, MD
Professor of Medicine, Infectious Diseases and Geographic Medicine, Stanford University School of Medicine, Stanford, California
Toxoplasma gondii

Shannon N. Moonah, MD, ScM
Assistant Professor of Medicine, Division of Infectious Diseases and International Health, University of Virginia, Charlottesville, Virginia
Entamoeba *Species, Including Amebic Colitis and Liver Abscess*

Thomas A. Moore, MD
Clinical Professor of Medicine, University of Kansas School of Medicine-Wichita, Wichita, Kansas
Drugs for Helminths

Philippe Moreillon, MD, PhD
Emeritus Professor, Department of Fundamental Microbiology, University of Lausanne, Lausanne, Switzerland
Staphylococcus aureus *(Including Staphylococcal Toxic Shock Syndrome)*

Janet Morgan, BGS
Program Director, Vaccine Research Group, Beth Israel Deaconess Medical Center, Boston, Massachusetts
Antiviral Agents: General Principles

J. Glenn Morris, Jr., MD, MPH&TM
Director, Emerging Pathogens Institute, University of Florida; Professor of Medicine (Infectious Diseases), University of Florida College of Medicine, Gainesville, Florida
Human Illness Associated With Harmful Algal Blooms

Jose M. Munita, MD
Director, Millennium Initiative for Collaborative Research On Bacterial Resistance (MICROB-R); Associate Professor, Infectious Diseases, Clinica Alemana Universidad del Desarrollo, Santiago, Chile; Adjunct Assistant Professor, Infectious Diseases, Faculty, Center for Antimicrobial Resistance and Microbial Genomics, University of Texas Health Science Center, Houston, Texas
Daptomycin and Quinupristin-Dalfopristin

Edward L. Murphy, MD, MPH
Professor Emeritus, Departments of Laboratory Medicine and Epidemiology/Biostatistics, University of California San Francisco School of Medicine; Senior Investigator, Vitalant Research Institute, San Francisco, California
Human T-Cell Leukemia Viruses (HTLV-1, HTLV-2)

Timothy F. Murphy, MD
SUNY Distinguished Professor, Clinical and Translational Research Center, University at Buffalo, State University of New York, Buffalo, New York
Moraxella catarrhalis, Kingella, *and Other Gram-Negative Cocci*
Haemophilus *Species, Including* H. influenzae *and* H. ducreyi *(Chancroid)*

Barbara E. Murray, MD
J. Ralph Meadows Professor and Director, Division of Infectious Diseases, Department of Internal Medicine and Department of Microbiology and Molecular Genetics, University of Texas Medical School at Houston, Houston, Texas
Daptomycin and Quinupristin-Dalfopristin
Glycopeptides (Vancomycin and Teicoplanin) and Lipoglycopeptides (Telavancin, Oritavancin, and Dalbavancin)
Enterococcus *Species,* Streptococcus gallolyticus *Group, and* Leuconostoc *Species*

Clinton K. Murray, MD
United States Forces Korea, Command Surgeon, Camp Humphreys, Korea; Professor of Medicine, Uniformed Services University of the Health Sciences, Bethesda, Maryland
Burns

Daniel M. Musher, MD
Distinguished Service Professor of Medicine, Professor of Molecular Virology and Microbiology, Baylor College of Medicine, Michael E. DeBakey Veterans Affairs Medical Center, Houston, Texas
Streptococcus pneumoniae

Eleftherios Mylonakis, MD
Dean's Professor of Medical Science, Chief, Infectious Diseases Division, Alpert Medical School of Brown University Rhode Island Hospital, Providence, Rhode Island
Listeria monocytogenes

Jerod L. Nagel, PharmD
Clinical Specialist, Infectious Diseases, University of Michigan Health System, Ann Arbor, Michigan
Metronidazole

Susanna Naggie, MD, MHS
Associate Professor of Medicine, Duke University School of Medicine, Durham, North Carolina
Hepatitis C

Esteban C. Nannini, MD
Associate Professor, Division of Infectious Diseases, School of Medicine, Universidad Nacional de Rosario; Independent Researcher, National Council for Scientific and Technical Research (CONICET), Argentina
Glycopeptides (Vancomycin and Teicoplanin) and Lipoglycopeptides (Telavancin, Oritavancin, and Dalbavancin)

Theodore E. Nash, MD
Principal Investigator, Clinical Parasitology Section, Laboratory of Parasitic Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland
Giardia lamblia
Visceral Larva Migrans and Other Uncommon Helminth Infections

William M. Nauseef, MD
Director, Iowa Inflammation Program; Professor of Medicine and Microbiology, Department of Medicine, Roy J. and Lucille A. Carver College of Medicine, University of Iowa; Iowa City Veterans Affairs Medical Center, Iowa City, Iowa
Granulocytic Phagocytes

Jennifer L. Nayak, MD
Associate Professor, Department of Pediatrics, Division of Pediatric Infectious Diseases, University of Rochester School of Medicine and Dentistry, University of Rochester Medical Center, Rochester, New York
Epiglottitis

Marguerite A. Neill, MD
Associate Professor of Medicine, Warren Alpert Medical School, Brown University, Providence, Rhode Island; Attending Physician, Division of Infectious Diseases, Memorial Hospital of Rhode Island, Pawtucket, Rhode Island
Other Pathogenic Vibrios

George E. Nelson, MD
Assistant Professor, Infectious Diseases, Vanderbilt University Medical Center, Nashville, Tennessee
Enterobacteriaceae

Joanna K. Nelson, MD
Clinical Assistant Professor, Infectious Disease and Geographic Medicine, Stanford University School of Medicine, Stanford, California
Bacterial Lung Abscess

Whitney J. Nesbitt, PharmD
Antimicrobial Stewardship Pharmacist, Pharmaceutical Services, Vanderbilt University Medical Center, Nashville, Tennessee
Macrolides and Clindamycin

M. Hong Nguyen, MD
University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania
Antifungal Drugs: Echinocandins

Judith A. O'Donnell, MD
Professor of Clinical Medicine, Division of Infectious Diseases, Perelman School of Medicine at the University of Pennsylvania; Chief, Division of Infectious Diseases, Penn Presbyterian Medical Center; Hospital Epidemiologist and Director, Department of Infection Prevention & Control and Healthcare Epidemiology, Penn Presbyterian Medical Center, Philadelphia, Pennsylvania
Topical Antibacterials

Christopher A. Ohl, MD
Professor of Medicine, Section on Infectious Diseases, Wake Forest School of Medicine; Medical Director, Center for Antimicrobial Utilization, Stewardship, and Epidemiology, Wake Forest Baptist Health, Winston-Salem, North Carolina
Infectious Arthritis of Native Joints

Pablo C. Okhuysen, MD
Professor of Infectious Diseases, Infection Control and Employee Health, University of Texas MD Anderson Cancer Center; Adjunct Professor of Infectious Diseases, Baylor College of Medicine; Adjunct Professor of Epidemiology, Human Genetics and Environmental Health, University of Texas School of Public Health; Adjunct Professor of Infectious Diseases, McGovern Medical School at the University of Texas Health Science Center at Houston, Houston, Texas
Sporothrix schenckii
Bacillary Dysentery: Shigella *and Enteroinvasive* Escherichia coli

Andrew B. Onderdonk, PhD
Brigham and Women's Hospital, Microbiology Laboratory, Boston, Massachusetts
Diseases Caused by Clostridium
Bacteroides, Prevotella, Porphyromonas, *and* Fusobacterium *Species (and Other Medically Important Anaerobic Gram-Negative Bacilli)*

Steven M. Opal, MD
Professor of Medicine, Infectious Disease Division, The Alpert Medical School of Brown University; Co-Director, Ocean State Clinical Coordinating Center at Rhode Island Hospital, Providence, Rhode Island
Molecular Mechanisms of Antibiotic Resistance in Bacteria

Walter A. Orenstein, MD
Professor of Medicine, Pediatrics, Global Health, and Epidemiology, Emory University; Associate Director, Emory Vaccine Center, Atlanta, Georgia
Immunization

Douglas R. Osmon, MD
Professor of Medicine, Department of Infectious Diseases, Mayo Clinic, Rochester, Minnesota
Osteomyelitis

Michael N. Oxman, MD
Professor of Medicine and Pathology, University of California San Diego School of Medicine; Staff Physician (Infectious Diseases), Medicine Service, Veterans Affairs San Diego Healthcare System, San Diego, California
Myocarditis and Pericarditis

Slobodan Paessler, DVM, PhD
Associate Professor, Department of Pathology, Director, Galveston National Laboratory Preclinical Studies Core, Director, Animal Biosafety Level 3, Institute for Human Infections and Immunity, University of Texas Medical Branch, Galveston, Texas
Lymphocytic Choriomeningitis Virus, Lassa Virus, and the South American Hemorrhagic Fevers (Arenaviruses)

Andrea V. Page, MSc, MD
Assistant Professor, Department of Medicine, University of Toronto; Staff Physician, Division of Infectious Diseases, Mount Sinai Hospital, Toronto, Ontario, Canada
Immunomodulators

Manjunath P. Pai, PharmD
Associate Professor, Department of Clinical Pharmacy, College of Pharmacy, University of Michigan, Ann Arbor, Michigan
Tables of Antiinfective Agent Pharmacology
Pharmacokinetics and Pharmacodynamics of Antiinfective Agents

Tara N. Palmore, MD
Chief, Hospital Epidemiology Service, Clinical Center, National Institutes of Health, Bethesda, Maryland
Infection Prevention and Control in the Health Care Setting

Raj Palraj, MBBS
Assistant Professor of Medicine, Mayo Clinic College of Medicine; Consultant, Infectious Diseases, Mayo Clinic, Rochester, Minnesota
Prosthetic Valve Endocarditis

Peter G. Pappas, MD
Professor of Medicine, Division of Infectious Diseases, University of Alabama at Birmingham, Birmingham, Alabama
Chronic Pneumonia

Daniel H. Paris, MD, PhD
Swiss Tropical and Public Health Institute, Basel, Switzerland; Faculty of Medicine, University of Basel, Switzerland; Mahidol-Oxford Tropical Medicine Research Unit, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand; Centre for Tropical Medicine and Global Health, Nuffield Department of Medicine, University of Oxford, Oxford, United Kingdom
Orientia tsutsugamushi *(Scrub Typhus)*

Tom Parks, MD
Postdoctoral Clinical Research Fellow, Faculty of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, London, United Kingdom; Postdoctoral Clinical Research Fellow, Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, United Kingdom; Specialty Registrar in Infectious Diseases, Hospital for Tropical Diseases, University College London Hospitals, London, United Kingdom
Human Genetics and Infection

Julie Parsonnet, MD
George DeForest Barnett Professor of Medicine, Medicine and Health Research and Policy, Stanford University, Stanford, California
Bacterial Lung Abscess

Mark Parta, MD, MPHTM
Acting Chief, Infectious Diseases Consult Service, Warren Grant Magnuson Clinical Center, National Institutes of Health; Clinical Research Directorate, Frederick National Laboratory for Cancer Research, Leidos Biomedical Research, Inc., Support to LCIM/ICMOB/NIAID (Transplant)
Pleural Effusion and Empyema

Mark S. Pasternack, MD
Associate Professor, Department of Pediatrics, Harvard Medical School; Chief, Pediatric Infectious Disease Unit, MassGeneral Hospital for Children, Massachusetts General Hospital, Boston, Massachusetts
Cellulitis, Necrotizing Fasciitis, and Subcutaneous Tissue Infections
Myositis and Myonecrosis
Lymphadenitis and Lymphangitis

Daniel M. Pastula, MD, MHS
Assistant Professor, Departments of Neurology, Medicine (Infectious Diseases), and Epidemiology, University of Colorado School of Medicine and Colorado School of Public Health, Aurora, Colorado
Coltiviruses (Colorado Tick Fever Virus) and Seadornaviruses

Robin Patel, MD
Elizabeth P. and Robert E. Allen Professor of Individualized Medicine, Professor of Medicine and Microbiology; Chair, Division of Clinical Microbiology; Director, Infectious Diseases Research Laboratory; Co-Director, Clinical Bacteriology Laboratory; Consultant, Divisions of Clinical Microbiology and Infectious Diseases; Mayo Clinic, Rochester, Minnesota
The Clinician and the Microbiology Laboratory: Test Ordering, Specimen Collection, and Result Interpretation

Thomas F. Patterson, MD
Professor, Department of Medicine/Infectious Diseases, The University of Texas Health Science Center, San Antonio, Texas
Aspergillus *Species*

Deborah Pavan-Langston, MD
Professor of Ophthalmology, Emerita, Harvard Medical School; Massachusetts Eye and Ear Infirmary, Boston, Massachusetts
Microbial Keratitis
Microbial Conjunctivitis

David A. Pegues, MD
Professor of Medicine, Division of Infectious Diseases, Perelman School of Medicine at the University of Pennsylvania; Medical Director, Healthcare Epidemiology, Infection Prevention and Control, Hospital of the University of Pennsylvania; Antimicrobial Management Program, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania
Salmonella *Species*

Stephen I. Pelton, MD
Professor of Pediatrics and Epidemiology, Pediatrics, Boston University Schools of Medicine and Public Health; Section of Pediatric Infectious Diseases, Pediatrics, Boston Medical Center, Boston, Massachusetts
Otitis Externa, Otitis Media, and Mastoiditis

Robert L. Penn, MD
Professor of Medicine, Infectious Diseases Section, Louisiana State University School of Medicine in Shreveport, Shreveport, Louisiana
Francisella tularensis *(Tularemia)*

John R. Perfect, MD
James B. Duke Professor of Medicine, Chief, Division of Infectious Diseases, Department of Medicine, Duke University Medical Center, Durham, North Carolina
Cryptococcosis (Cryptococcus neoformans *and* Cryptococcus gattii)

Ryan Perkins, MD
Clinical Fellow, Harvard Medical School, Division of Pulmonary Medicine, Boston Children's Hospital; Division of Pulmonary and Critical Care Medicine, Brigham and Women's Hospital, Boston, Massachusetts
Cystic Fibrosis

Stanley Perlman, MD, PhD
Professor, Department of Microbiology and Immunology, and of Pediatrics, University of Iowa Carver College of Medicine, Iowa City, Iowa
Coronaviruses, Including Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS)

Brett W. Petersen, MD, MPH
Epidemiology Team Lead, Poxvirus and Rabies Branch Division of High Consequence Pathogens and Pathology, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia
Orthopoxviruses: Vaccinia (Smallpox Vaccine), Variola (Smallpox), Monkeypox, and Cowpox
Other Poxviruses That Infect Humans: Parapoxviruses (Including Orf Virus), Molluscum Contagiosum, and Yatapoxviruses

William A. Petri, Jr., MD, PhD
Wade Hampton Frost Professor of Epidemiology, University of Virginia; Chief, Division of Infectious Disease and International Health, University of Virginia Health System, Charlottesville, Virginia
Introduction to Protozoal Diseases
Entamoeba *Species, Including Amebic Colitis and Liver Abscess*

Cathy A. Petti, MD
CEO, HealthSpring Global, Inc., Bradenton, Florida
Streptococcus anginosus *Group*

Jennifer A. Philips, MD, PhD
Division of Infectious Diseases, Department of Medicine, Department of Molecular Microbiology, Washington University School of Medicine, St. Louis, Missouri
Introduction to Bacteria and Bacterial Diseases

Julie V. Philley, MD
Associate Professor of Medicine, Chair, Department of Medicine, Division Chief, Pulmonary and Critical Care Medicine, University of Texas Health Science Center, Tyler, Texas
Antimycobacterial Agents

Michael Phillips, MD
Hospital Epidemiologist and Director of Infection Prevention and Control, NYU Langone Health; Clinical Associate Professor, Department of Medicine, Division of Infectious Diseases and Immunology, NYU School of Medicine, New York, New York
Acinetobacter *Species*

Larry K. Pickering, MD
Senior Advisor to the Director, National Center for Immunization and Respiratory Diseases; Executive Secretary, Advisory Committee on Immunization Practices, Centers for Disease Control and Prevention, Atlanta, Georgia
Immunization

Peter Piot, MD, PhD
Director and Professor of Global Health, London School of Hygiene and Tropical Medicine, London, United Kingdom
Global Perspectives on Human Immunodeficiency Virus Infection and Acquired Immunodeficiency Syndrome

Jason M. Pogue, PharmD
Clinical Pharmacist Specialist, Infectious Diseases, Sinai Grace Hospital, Detroit, Michigan
Polymyxins (Polymyxin B and Colistin)

Bruce Polsky, MD
Associate Dean, Faculty, Professor and Chairman, Department of Medicine, NYU Long Island School of Medicine and NYU Winthrop Hospital, Mineola, New York
Nutrition, Immunity, and Infection

Aurora Pop-Vicas, MD, MPH
Assistant Professor of Medicine, Infectious Disease Division, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin
Molecular Mechanisms of Antibiotic Resistance in Bacteria

Cynthia Portal-Celhay, MD, PhD
Assistant Professor of Medicine and Microbiology, Division of Infectious Diseases, New York University School of Medicine, New York, New York
Rifamycins

John H. Powers III, MD
Professor of Clinical Medicine, Department of Medicine, George Washington University School of Medicine, Washington, DC; Senior Medical Scientist, Division of Clinical Research, SAIC in support of National Institute of Allergy and Infectious Diseases, National Institute of Health, Bethesda, Maryland
Designing and Interpreting Clinical Studies in Infectious Diseases

Richard N. Price, MD
Professor, Global Health Division, Menzies School of Health Research and Charles Darwin University, Darwin, Northern Territory, Australia; Professor, Centre for Tropical Medicine, Nuffield Department of Clinical Medicine, University of Oxford, Oxford, United Kingdom
Antimalarial Drugs

Yok-Ai Que, MD, PhD
Associate Professor, Faculty of Medicine, University of Bern and Senior Physician, Department of Intensive Care Medicine, Inselspital Bern University Hospital, Bern, Switzerland
Staphylococcus aureus *(Including Staphylococcal Toxic Shock Syndrome)*

Justin D. Radolf, MD
Professor, Departments of Medicine, Pediatrics, Immunology, Genetics and Genome Sciences and Molecular Biology and Biophysics, University of Connecticut School of Medicine, Farmington, Connecticut; Director of Research, Department of Medicine; Senior Scientific Advisor, Connecticut Children's Medical Center, Hartford, Connecticut
Syphilis (Treponema pallidum)

Sanjay Ram, MB, BS
Professor of Medicine, Division of Infectious Diseases and Immunology, University of Massachusetts Medical Center, Worcester, Massachusetts
Complement and Deficiencies

Lalita Ramakrishnan, MD, PhD
Professor of Immunology and Infectious Diseases, University of Cambridge, Cambridge, United Kingdom
A Molecular Perspective of Microbial Pathogenicity

Didier Raoult, MD, PhD
IHU Meditérranée Infection, MEPHI, Aix Marseille University, Marseille, France
Introduction to Rickettsioses, Ehrlichioses, and Anaplasmoses
Rickettsia akari *(Rickettsialpox)*
Coxiella burnetii *(Q Fever)*

Jonathan I. Ravdin, MD
Milwaukee, Wisconsin
Introduction to Protozoal Diseases

Annette C. Reboli, MD
Dean, Professor of Medicine, Department Medicine, Cooper Medical School of Rowan University, Camden, New Jersey
Other Coryneform Bacteria, Arcanobacterium haemolyticum, *and Rhodococci*
Erysipelothrix rhusiopathiae

Henry Redel, MD
Clinical Instructor, Department of Medicine, Rutgers Robert Wood Johnson Medical School, New Brunswick, New Jersey
Nutrition, Immunity, and Infection

Marvin S. Reitz, Jr., PhD
Professor, Institute of Human Virology, University of Maryland School of Medicine, Baltimore, Maryland
Human Immunodeficiency Viruses

David A. Relman, MD
Thomas C. and Joan M. Merigan Professor, Departments of Medicine and of Microbiology & Immunology, Stanford University School of Medicine, Stanford, California; Chief of Infectious Diseases, Veterans Affairs Palo Alto Health Care System, Palo Alto, California
A Molecular Perspective of Microbial Pathogenicity

Hilary E.L. Reno, MD, PhD
Assistant Professor, Medicine, Washington University in St. Louis, St. Louis, Missouri
Klebsiella granulomatis *(Donovanosis, Granuloma Inguinale)*

Ángela Restrepo-Moreno, MSc, PhD
Former Scientific Director, Senior Researcher, and Head, Medical and Experimental Mycology Unit, Corporacion para Investigaciones Biologicas, Medellín, Antioquia, Colombia
Paracoccidioidomycosis

John H. Rex, MD
Chief Medical Officer, F2G Limited, Eccles, Cheshire, United Kingdom; Adjunct Professor of Medicine, Infectious Diseases, McGovern Medical School at The University of Texas Health Science Center at Houston, Houston, Texas
Sporothrix schenckii

Elizabeth G. Rhee, MD
Director, Department of Clinical Pharmacology, Merck Research Laboratories, Kenilworth, NJ
Adenoviruses

Norbert J. Roberts, Jr., MD
Professor Emeritus, Department of Internal Medicine, Division of Infectious Diseases, University of Texas Medical Branch, Galveston, Texas; Adjunct Professor, Department of Medicine, Division of Infectious Diseases and Immunology, New York University School of Medicine, New York, New York
Hyperbaric Oxygen

Andrej A. Romanovsky, MD, PhD
Professor, Thermoregulation and Systemic Inflammation Laboratory (FeverLab), St. Joseph's Hospital and Medical Center, Phoenix, Arizona
Temperature Regulation and the Pathogenesis of Fever

José R. Romero, MD
Horace C. Cabe Professor of Infectious Diseases, Department of Pediatrics, University of Arkansas for Medical Sciences; Director, Pediatric Infectious Diseases Section, Department of Pediatrics, Arkansas Children's Hospital; Director, Clinical Trials Research, Arkansas Children's Research Institute, Little Rock, Arkansas
Poliovirus
Parechoviruses
Coxsackieviruses, Echoviruses, and Numbered Enteroviruses (EV-A71, EVD-68, EVD-70)
Introduction to the Human Enteroviruses and Parechoviruses

Stacey R. Rose, MD
Assistant Professor, Department of Medicine, Section of Infectious Diseases; Assistant Dean of Clinical Curriculum, School of Medicine, Baylor College of Medicine, Houston, Texas
Bartonella, *Including Cat-Scratch Disease*

Ronald Rosenberg, ScD
Associate Director, Division of Vector-Borne Diseases, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention, Fort Collins, Colorado
Emerging and Reemerging Infectious Disease Threats

Alan L. Rothman, MD
Research Professor, Cellular and Molecular Biology, The University of Rhode Island, Kingston, Rhode Island
Flaviviruses (Dengue, Yellow Fever, Japanese Encephalitis, West Nile Encephalitis, Usutu Encephalitis, St. Louis Encephalitis, Tick-Borne Encephalitis, Kyasanur Forest Disease, Alkhurma Hemorrhagic Fever, Zika)

Craig R. Roy, PhD
Professor of Microbial Pathogenesis, Department of Microbial Pathogenesis, Yale University School of Medicine, New Haven, Connecticut
Legionnaires' Disease and Pontiac Fever

Kathryn L. Ruoff, PhD
Research Scientist, O'Toole Lab, Department of Microbiology and Immunology, Geisel School of Medicine at Dartmouth, Hanover, New Hampshire
Classification of Streptococci

Mark E. Rupp, MD
Professor and Chief, Department of Infectious Diseases, University of Nebraska Medical Center; Medical Director, Infection Control and Epidemiology, The Nebraska Medical Center, Omaha, Nebraska
Mediastinitis
Staphylococcus epidermidis *and Other Coagulase-Negative Staphylococci*

Charles E. Rupprecht, VMD, MS, PhD
LYSSA LLC, Atlanta, Georgia
Rabies (Rhabdoviruses)

Thomas A. Russo, MD, CM
Professor of Medicine, and Microbiology and Immunology, Division of Infectious Diseases, University at Buffalo-SUNY Jacobs School of Medicine and Biomedical Sciences; Staff Physician, Veterans Administration Western New York Health Care System, Buffalo, New York
Agents of Actinomycosis

William A. Rutala, MS, PhD, MPH
Professor of Medicine, Director, Statewide Program for Infection Control and Epidemiology, University of North Carolina School of Medicine, Chapel Hill, North Carolina
Disinfection, Sterilization, and Control of Hospital Waste

Edward T. Ryan, MD
Director, Global Infectious Diseases, Massachusetts General Hospital; Professor of Medicine, Harvard Medical School; Professor of Immunology, Professor of Immunology and Infectious Diseases, Harvard T.H. Chan School of Public Health, Harvard School of Public Health, Boston, Massachusetts
Typhoid Fever, Paratyphoid Fever, and Typhoidal Fevers
Vibrio cholerae

Mohammad M. Sajadi, MD
Associate Professor of Medicine, Institute of Human Virology, University of Maryland School of Medicine, Baltimore, Maryland
Temperature Regulation and the Pathogenesis of Fever

Juan C. Salazar, MD, MPH
Professor and Chair, Department of Pediatrics, University of Connecticut School of Medicine, Farmington, Connecticut; Physician-in-Chief, Connecticut Children's Medical Center, Hartford, Connecticut
Syphilis (Treponema pallidum)

Paul G. Saleeb, MD
Assistant Professor of Medicine, Institute of Human Virology, Department of Medicine, University of Maryland School of Medicine, Baltimore, Maryland
Corynebacterium diphtheriae *(Diphtheria)*

Juan Carlos Sarria, MD
Professor of Medicine, Department of Internal Medicine, Division of Infectious Diseases, University of Texas Medical Branch, Galveston, Texas
Hyperbaric Oxygen

Maria C. Savoia, MD
Dean for Medical Education, Professor of Medicine, University of California San Diego School of Medicine, La Jolla, California
Myocarditis and Pericarditis

Paul E. Sax, MD
Professor of Medicine, Harvard Medical School; Clinical Director, Division of Infectious Diseases and Human Immunodeficiency Virus Program, Brigham and Women's Hospital, Boston, Massachusetts
Pulmonary Manifestations of Human Immunodeficiency Virus Infection

Joshua T. Schiffer, MD, MSc
Associate Professor, Department of Medicine, University of Washington; Associate Member, Vaccine and Infectious Diseases Division, Fred Hutchinson Cancer Research Center, Seattle, Washington
Herpes Simplex Virus

David Schlossberg, MD
Professor, The Lewis Katz School of Medicine at Temple University; Medical Director, Tuberculosis Control Program, Philadelphia Department of Public Health, Philadelphia, Pennsylvania
Adjunct Professor, The Perelman School of Medicine at the University of Pennsylvania
Psittacosis (*Due to* Chlamydia psittaci)

Thomas Schneider, MD, PhD
Professor of Infectious Diseases, Charite University Hospital, Benjamin Franklin Campus, Berlin, Germany
Whipple Disease

Jane R. Schwebke, MD
Professor of Medicine, Medicine/Infectious Diseases, University of Alabama at Birmingham, Birmingham, Alabama
Trichomonas vaginalis

Cynthia L. Sears, MD
Professor of Medicine, Divisions of Infectious Diseases and Gastroenterology, Johns Hopkins University School of Medicine, Baltimore, Maryland
Prebiotics, Probiotics, and Synbiotics

Leopoldo N. Segal, MD
Assistant Professor, Department of Medicine, New York University School of Medicine, New York, New York
Acute Exacerbations of Chronic Obstructive Pulmonary Disease

Parham Sendi, MD
Institute for Infectious Diseases, University of Bern, Bern, Switzerland
Orthopedic Implant–Associated Infections

Kent A. Sepkowitz, MD
Deputy Physician-in-Chief, Quality and Safety, Memorial Sloan Kettering Cancer Center; Professor of Medicine, Weill-Cornell Medical College, New York, New York
Health Care–Acquired Hepatitis

Alexey Seregin, PhD
Graduate Assistant, Pathology Education, University of Texas Medical Branch, Galveston, Texas
Lymphocytic Choriomeningitis Virus, Lassa Virus, and the South American Hemorrhagic Fevers (Arenaviruses)

Stanford T. Shulman, MD
Virginia H. Rogers Professor of Pediatric Infectious Diseases, Northwestern University Feinberg School of Medicine; Chief, Division of Infectious Diseases, Department of Pediatrics, Children's Memorial Hospital, Chicago, Illinois
Nonsuppurative Poststreptococcal Sequelae: Rheumatic Fever and Glomerulonephritis

George K. Siberry, MD, MPH
Senior Technical Advisor for Pediatrics, Office of the Global AIDS Coordinator (PEPFAR), US Department of State, Washington, DC
Pediatric Human Immunodeficiency Virus Infection

Omar K. Siddiqi, MD, MPH
Assistant Professor of Neurology, Harvard Medical School; Department of Neurology, Beth Israel Deaconess Medical Center, Boston, Massachusetts; Honorary Lecturer, Department of Medicine, University of Zambia School of Medicine, Lusaka, Zambia
Neurologic Diseases Caused by Human Immunodeficiency Virus Type 1 and Opportunistic Infections

Costi D. Sifri, MD
Professor of Medicine, Division of Infectious Diseases and International Health, University of Virginia School of Medicine; Hospital Epidemiologist, Director, Hospital Epidemiology/Infection Prevention & Control, University of Virginia Health System, Charlottesville, Virginia
Appendicitis
Infections of the Liver and Biliary System (Liver Abscess, Cholangitis, Cholecystitis)
Diverticulitis and Neutropenic Enterocolitis

Michael S. Simberkoff, MD
Professor of Medicine, Division of Infectious Diseases and Immunology, New York University Langone Medical Center, New York, New York
Mycoplasma pneumoniae *and Atypical Pneumonia*

Francesco Simonetti, MD
Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland
Diagnosis of Human Immunodeficiency Virus Infection

Nina Singh, MD
Professor of Medicine, Department of Medicine, Division of Infectious Diseases, University of Pittsburgh and Pittsburgh VA Healthcare System, Pittsburgh, Pennsylvania
Infections in Solid-Organ Transplant Recipients

Upinder Singh, MD
Professor of Medicine, Departments of Infectious Diseases, Microbiology and Immunology, Stanford School of Medicine, Stanford, California
Free-Living Amebae

A. George Smulian, MB, BCh
Professor, Infectious Disease Division, University of Cincinnati College of Medicine; Infectious Disease Section, Cincinnati VA Medical Center, Cincinnati, Ohio
Pneumocystis *Species*

Jack D. Sobel, MD
Professor of Medicine, Infectious Diseases, Wayne State University School of Medicine, Detroit, Michigan
Urinary Tract Infections

M. Rizwan Sohail, MD
Professor of Medicine, Division of Infectious Diseases, Department of Medicine, Mayo Clinic College of Medicine and Science, Rochester, Minnesota
Infections of Nonvalvular Cardiovascular Devices

Tania C. Sorrell, MB BS, MD
Director, Marie Bashir Institute for Infectious Diseases and Biosecurity, University of Sydney, Sydney; Director, Infectious Diseases and Sexual Health, Western Sydney Local Health District, Westmead; Centre for Infectious Diseases and Microbiology, Westmead Institute for Medical Research, Westmead, New South Wales, Australia
Nocardia *Species*

Brad Spellberg, MD
Chief Medical Officer, LAC+USC Medical Center; Professor of Clinical Medicine and Associate Dean, Departments of Medicine and Molecular Microbiology & Immunology, Keck School of Medicine of USC, Los Angeles, California
Principles of Antiinfective Therapy

James M. Steckelberg, MD
Professor of Medicine, Consultant, Division of Infectious Diseases, Mayo Clinic, Rochester, Minnesota
Osteomyelitis

Allen C. Steere, MD
Professor of Medicine, Harvard Medical School, Harvard University; Director, Translational Research in Rheumatology, Massachusetts General Hospital, Boston, Massachusetts
Lyme Disease (Lyme Borreliosis) Due to Borrelia burgdorferi

James P. Steinberg, MD
Professor of Medicine, Division of Infectious Diseases, Emory University School of Medicine; Chief Medical Officer, Emory University Hospital Midtown, Atlanta, Georgia
Other Gram-Negative and Gram-Variable Bacilli

David S. Stephens, MD
Stephen W. Schwarzmann Distinguished Professor of Medicine, Chair, Department of Medicine, Emory University School of Medicine; Vice President for Research, Woodruff Health Sciences Center, Atlanta, Georgia
Neisseria meningitidis

Kathryn E. Stephenson, MD, MPH
Assistant Professor of Medicine, Harvard Medical School; Ragon Institute of MGH, MIT, and Harvard; Center for Virology and Vaccine Research, Beth Israel Deaconess Medical Center, Boston, Massachusetts
Adenoviruses

Timothy R. Sterling, MD
Professor of Medicine, Division of Infectious Diseases, Vanderbilt University School of Medicine, Nashville, Tennessee
General Clinical Manifestations of Human Immunodeficiency Virus Infection (Including Acute Retroviral Syndrome and Oral, Cutaneous, Renal, Ocular, Metabolic, and Cardiac Diseases)
Mycobacterium tuberculosis

David A. Stevens, MD
President, California Institute for Medical Research, San Jose, California; Professor of Medicine, Stanford University, Stanford, California
Antifungal Agents: Amphotericin B

Dennis L. Stevens, MD, PhD
Professor of Medicine, University of Washington, Seattle, Washington
Streptococcus pyogenes

Bradley P. Stoner, MD, PhD
Associate Professor, Departments of Anthropology and Medicine, Washington University in St. Louis, St. Louis, Missouri
Klebsiella granulomatis *(Donovanosis, Granuloma Inguinale)*

Jacob Strahilevitz, MD
Senior Lecturer in Clinical Microbiology, Hebrew University; Attending Physician, Clinical Microbiology and Infectious Diseases, Hadassah Medical Center, Jerusalem, Israel
Quinolones

Charles W. Stratton IV, MD
Associate Professor of Pathology and Medicine, Vanderbilt University School of Medicine; Director, Clinical Microbiology Laboratory, Vanderbilt University Medical Center, Nashville, Tennessee
Streptococcus anginosus *Group*

Luke C. Strnad, MD
Assistant Professor, Department of Medicine, Division of Infectious Diseases, Oregon Health & Science University; Assistant Professor of Epidemiology Programs, Oregon Health & Science University and Portland State University School of Public Health, Portland, Oregon
Mycobacterium avium *Complex*

Kathryn N. Suh, MD, MSc
Associate Professor of Medicine, Division of Infectious Diseases, University of Ottawa, The Ottawa Hospital, Ottawa, Ontario, Canada
Cyclospora cayetanensis, Cystoisospora belli, Sarcocystis *Species*, Balantidium coli, *and* Blastocystis *Species*

Mark S. Sulkowski, MD
Professor of Medicine, Johns Hopkins University School of Medicine, Medical Director, Viral Hepatitis Center, Johns Hopkins Hospital, Baltimore, Maryland
Gastrointestinal, Hepatobiliary, and Pancreatic Manifestations of Human Immunodeficiency Virus Infection

Morton N. Swartz, MD†
Former Associate Firm Chief, Infectious Diseases Unit, Massachusetts General Hospital, Boston, Massachusetts
Cellulitis, Necrotizing Fasciitis, and Subcutaneous Tissue Infections

Naasha J. Talati, MD, MSCR
Clinical Assistant Professor, Department of Medicine, Division of Infectious Diseases, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania
Topical Antibacterials

Thomas R. Talbot, MD, MPH
Professor, Medicine, Vanderbilt University School of Medicine; Chief Hospital Epidemiologist, Vanderbilt University Medical Center, Nashville, Tennessee
Surgical Site Infections and Antimicrobial Prophylaxis

C. Sabrina Tan, MD
Assistant Professor of Medicine, Harvard Medical School, Beth Israel Deaconess Medical Center, Boston, Massachusetts
JC, BK, and Other Polyomaviruses: Progressive Multifocal Leukoencephalopathy (PML)

Ming Tan, MD
Professor of Medicine and Microbiology & Molecular Genetics, University of California Irvine School of Medicine, Irvine, California
Chlamydia trachomatis *(Trachoma and Urogenital Infections)*

Aaron J. Tande, MD
Assistant Professor, Infectious Diseases, Mayo Clinic, Rochester, Minnesota
Osteomyelitis

Brenda L. Tesini, MD
Assistant Professor, Medicine and Pediatrics, University of Rochester, Rochester, New York
Acute Laryngitis

Chloe Lynne Thio, MD
Professor of Medicine, Internal Medicine/Division of Infectious Diseases, Johns Hopkins University School of Medicine, Baltimore, Maryland
Hepatitis B Virus
Hepatitis Delta Virus

Stephen J. Thomas, MD
Professor of Medicine and Microbiology & Immunology, Chief, Division of Infectious Diseases, Director, Institute for Global Health and Translational Science, Upstate Medical University, State University of New York, Syracuse, New York
Flaviviruses (Dengue, Yellow Fever, Japanese Encephalitis, West Nile Encephalitis, Usutu Encephalitis, St. Louis Encephalitis, Tick-Borne Encephalitis, Kyasanur Forest Disease, Alkhurma Hemorrhagic Fever, Zika)

George R. Thompson III, MD
Associate Professor of Medicine, Department of Internal Medicine, Division of Infectious Diseases, Department of Medical Microbiology and Immunology, University of California-Davis Health, Sacramento, California
Aspergillus *Species*
Antifungal Drugs: Azole

Anna R. Thorner, MD
Assistant Professor of Medicine, Part-Time, Department of Medicine, Harvard Medical School; Associate Physician, Division of Infectious Diseases, Brigham and Women's Hospital and Dana-Farber Cancer Institute, Boston, Massachusetts
Zoonotic Paramyxoviruses: Nipah, Hendra, and Menangle Viruses

Ángela Ma. Tobón-Orozco, MD
Professor, Internal Medicine, Instituto Colombiano de Medicina Tropical, Universidad CES, Sabaneta, Antioquia, Colombia
Paracoccidioidomycosis

Edmund C. Tramont, MD
Associate Director, Special Projects, Division of Clinical Research, National Institutes of Health, Bethesda, Maryland
Innate (General or Nonspecific) Host Defense Mechanisms
Syphilis (Treponema pallidum)

Barbara W. Trautner, MD, PhD
Center for Innovations in Quality, Effectiveness, and Safety (IQuESt), Michael E. DeBakey Veterans Affairs Medical Center; Associate Professor, Department of Medicine, Section of Health Services Research, Baylor College of Medicine, Houston, Texas
Health Care–Associated Urinary Tract Infections

John J. Treanor, MD
Emeritus Professor, University of Rochester Medical Center, Rochester, New York
Astroviruses and Picobirnaviruses
Influenza Viruses, Including Avian Influenza and Swine Influenza
Noroviruses and Sapoviruses (Caliciviruses)

Hirsh D. Trivedi, MD
Division of Gastroenterology and Hepatology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts
Hepatitis E Virus

Jason Trubiano, MD
Infectious Diseases Department, Austin Health; Department of Medicine, University of Melbourne, Melbourne, Australia
Fusidic Acid

Athe M.N. Tsibris, MD, MS
Assistant Professor in Medicine, Division of Infectious Diseases, Harvard Medical School, Brigham and Women's Hospital, Boston, Massachusetts
Antiretroviral Therapy for Human Immunodeficiency Virus Infection

†Deceased.

Allan R. Tunkel, MD, PhD
Professor of Medicine and Medical Science, Senior Associate Dean for Medical Education, Brown University; Warren Alpert Medical School, Providence, Rhode Island
Approach to the Patient With Central Nervous System Infection
Brain Abscess
Subdural Empyema, Epidural Abscess, and Suppurative Intracranial Thrombophlebitis
Acute Meningitis
Cerebrospinal Fluid Shunt and Drain Infections

Kenneth L. Tyler, MD
Louise Baum Endowed Chair and Chairman of Neurology. Professor of Medicine and Immunology-Microbiology, University of Colorado School of Medicine, Aurora, Colorado
Encephalitis
Orthoreoviruses and Orbiviruses
Coltiviruses
Prions and Prion Disease of the Central Nervous System (Transmissible Neurodegenerative Diseases)

Ahmet Z. Uluer, DO, MPH
Assistant Professor of Pediatrics, Department of Pediatrics, Harvard Medical School; Director, Adult Cystic Fibrosis Program, Division of Pulmonary Medicine, Boston Children's Hospital; Director, Adult Cystic Fibrosis Program, Division of Pulmonary and Critical Care Medicine, Brigham and Women's Hospital, Boston, Massachusetts
Cystic Fibrosis

Marguerite A. Urban, MD
Infectious Diseases Division, University of Rochester School of Medicine and Dentistry, Rochester, New York
Urethritis

Celalettin Ustun, MD
Professor of Medicine, Division of Hematology, Oncology and Cell Therapy, Section Chief, Bone Marrow and Stem Cell Transplant, Rush Medical College, Chicago, Illinois
Infections in Recipients of Hematopoietic Stem Cell Transplants

Timothy M. Uyeki, MD
Chief Medical Officer, Influenza Division, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia; Associate Clinical Professor, Department of Pediatrics, University of California, San Francisco, San Francisco, California
Emerging and Reemerging Infectious Disease Threats

Diederik van de Beek, MD, PhD
Neurologist, Department of Neurology, Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands
Acute Meningitis

Tom van der Poll, MD, PhD
Professor, Division of Infectious Diseases and Center for Experimental and Molecular Medicine, Amsterdam University Medical Centers, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands
Sepsis and Septic Shock

Walter J.F.M. van der Velden, MD, PhD
Consultant and Lecturer, Department of Haematology, Radboud University Medical Centre, Nijmegen, The Netherlands
Infections in the Immunocompromised Host: General Principles

Trevor C. Van Schooneveld, MD
Associate Professor, Division of Infectious Diseases, Department of Internal Medicine, University of Nebraska Medical Center; Medical Director, Antimicrobial Stewardship Program, The Nebraska Medical Center, Omaha, Nebraska
Mediastinitis

Edouard Vannier, PharmD, PhD
Assistant Professor of Medicine, Division of Geographic Medicine & Infectious Diseases, Tufts Medical Center & Tufts University School of Medicine, Boston, Massachusetts
Babesia *Species*

Claudia Vellozzi, MD, MPH
Director, Transitions of Care
Grady Health System
Atlanta, Georgia
Hepatitis A Virus

James Versalovic, MD, PhD
Professor, Baylor College of Medicine; Pathologist-in-Chief, Texas Children's Hospital, Houston, Texas
The Human Microbiome of Local Body Sites and Their Unique Biology

Vini Vijayan, MD
Associate Professor of Pediatrics, Section of Infectious Diseases, University of Arkansas for Medical Sciences, Little Rock, Arkansas
Parechoviruses

Claudio Viscoli, MD
Division of Infectious Diseases, Department of Health Sciences (DISSAL), University of Genoa; IRCCS Ospedale Policlinico San Martino, Genoa, Italy
Prophylaxis and Empirical Therapy of Infection in Cancer Patients

Ellen R. Wald, MD
Alfred Dorrance Daniels Professor on Diseases of Children, University of Wisconsin School of Medicine and Public Health; Pediatrician-in-Chief, American Family Children's Hospital, Madison, Wisconsin
Sinusitis

Matthew K. Waldor, MD, PhD
Edward H. Kass Professor of Medicine, Harvard Medical School, Division of Infectious Diseases, Brigham and Women's Hospital, Boston, Massachusetts
Vibrio cholerae

David H. Walker, MD
Professor, Department of Pathology, University of Texas Medical Branch; Executive Director, Center for Biodefense and Emerging Infectious Diseases, Galveston, Texas
Rickettsia rickettsii and Other Spotted Fever Group Rickettsiae (Rocky Mountain Spotted Fever and Other Spotted Fevers)
Rickettsia prowazekii *(Epidemic or Louse-Borne Typhus)*
Rickettsia typhi *(Murine Typhus)*
Ehrlichia chaffeensis *(Human Monocytotropic Ehrlichiosis),* Anaplasma phagocytophilum *(Human Granulocytotropic Anaplasmosis), and Other Anaplasmataceae*

Richard J. Wallace, Jr., MD
Professor of Medicine, John Chapman Professorship in Microbiology, Chairman, Department of Microbiology, University of Texas Health Science Center, Tyler, Texas
Antimycobacterial Agents
Infections Caused by Nontuberculous Mycobacteria Other Than Mycobacterium avium *Complex*

Edward E. Walsh, MD
Professor of Medicine, Department of Infectious Diseases, University of Rochester School of Medicine and Dentistry, Rochester, New York
Acute Bronchitis
Respiratory Syncytial Virus

Stephen R. Walsh, MD
Assistant Professor of Medicine, Harvard Medical School, Beth Israel Deaconess Medical Center, Boston, Massachusetts
Miscellaneous Antiviral Agents (Interferons, Tecovirimat, Imiquimod, Pocapavir, Pleconaril)

Peter D. Walzer, MD, MSc
Emeritus Professor, Internal Medicine, University of Cincinnati College of Medicine, Cincinnati, Ohio
Pneumocystis *Species*

Christine A. Wanke, MD
Professor Emerita, Departments of Medicine and Public Health, Tufts University School of Medicine, Boston, Massachusetts
Tropical Sprue and Environmental Enteric Dysfunction

Honorine D. Ward, MD
Professor, Division of Geographic Medicine and Infectious Diseases, Tufts University School of Medicine, Boston, Massachusetts
Tropical Sprue and Environmental Enteric Dysfunction

Cirle A. Warren, MD
Associate Professor of Medicine, Infectious Diseases, and International Health, University of Virginia School of Medicine, Charlottesville, Virginia
Acute Dysentery Syndromes (Diarrhea With Fever)

Ronald G. Washburn, MD
Professor of Medicine, Division of Infectious Diseases, Medical University of South Carolina; Chief, Infectious Diseases, Department of Medicine, Ralph H. Johnson VA Medical Center, Charleston, South Carolina
Rat-Bite Fever: Streptobacillus moniliformis *and* Spirillum minus

Valerie Waters, MD, MSc
Associate Professor, Department of Pediatrics, Division of Infectious Diseases, Hospital for Sick Children, Toronto, Canada
Bordetella pertussis

Richard R. Watkins, MD
Professor of Internal Medicine, Northeast Ohio Medical University, Rootstown, Ohio; Attending Physician, Division of Infectious Diseases, Cleveland Clinic Akron General, Akron, Ohio
Yersinia enterocolitica *and* Yersinia pseudotuberculosis

Matthew R. Watts, MBBS, PhD
Infectious Diseases Physician and Medical Microbiologist, Centre for Infectious Diseases and Microbiology, Westmead Hospital, Westmead; Institute of Clinical Pathology and Medical Research, New South Wales Health – Pathology, Westmead; Clinical Senior Lecturer, Sydney Medical School, University of Sydney, Sydney, New South Wales, Australia
Nocardia *Species*

Jill Weatherhead, MD
Assistant Professor of Infectious Diseases, Pediatric Infectious Diseases and Tropical Medicine, National School of Tropical Medicine, Baylor College of Medicine, Houston, Texas
Intestinal Nematodes (Roundworms)

David J. Weber, MD, MPH
Professor of Medicine, Pediatrics, and Epidemiology, University of North Carolina at Chapel Hill School of Medicine; Associate Chief of Staff and Medical Director, Hospital Epidemiology and Occupational Health, University of North Carolina Health Care, Chapel Hill, North Carolina
The Acutely Ill Patient With Fever and Rash
Disinfection, Sterilization, and Control of Hospital Waste

Michael D. Weiden, MD
Associate Professor, Departments of Medicine and Environmental Medicine, New York University School of Medicine, NYU Langone Medical Center, New York, New York
Acute Exacerbations of Chronic Obstructive Pulmonary Disease

Geoffrey A. Weinberg, MD
Professor of Pediatrics, Department of Pediatrics, University of Rochester School of Medicine and Dentistry; Clinical Director, Infectious Diseases and Pediatric HIV Program, Golisano Children's Hospital; University of Rochester Medical Center, Rochester, New York
Epiglottitis
Pediatric Human Immunodeficiency Virus Infection

Louis M. Weiss, MD, MPH
Professor of Pathology, Division of Parasitology and Tropical Medicine, Professor of Medicine, Division of Infectious Diseases, Albert Einstein College of Medicine, Bronx, New York
Microsporidiosis

Thomas E. Wellems, MD, PhD
Chief, Laboratory of Malaria and Vector Research, Chief, Malaria Genetics Section, LMVR, National Institute of Allergy and Infectious Diseases, Rockville, Maryland
Malaria (Plasmodium *Species*)

A. Clinton White, Jr., MD
Professor, Infectious Disease Division, Department of Internal Medicine, University of Texas Medical Branch, Galveston, Texas
Cryptosporidiosis (Cryptosporidium *Species*)

Richard J. Whitley, MD
Distinguished Professor of Pediatrics, Loeb Eminent Scholar Chair in Pediatrics, Professor of Microbiology, Medicine, and Neurosurgery, Department of Pediatrics, University of Alabama at Birmingham, Birmingham, Alabama
Chickenpox and Herpes Zoster (Varicella-Zoster Virus)

Willem Joost Wiersinga, MD, PhD
Professor, Division of Infectious Diseases and Center for Experimental and Molecular Medicine, Amsterdam University Medical Centers, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands
Sepsis and Septic Shock

Brett Williams, MD
Assistant Professor of Internal Medicine, Rush University, Chicago, Illinois
Rabies (Rhabdoviruses)

Walter R. Wilson, MD
Professor of Medicine, Mayo Clinic College of Medicine; Consultant, Infectious Diseases, Mayo Clinic, Rochester, Minnesota
Prosthetic Valve Endocarditis
Infections of Nonvalvular Cardiovascular Devices

Dean L. Winslow, MD
Professor, Medicine, Stanford University School of Medicine, Stanford, California
Endemic Treponematoses

Kevin L. Winthrop, MD, MPH
Professor of Infectious Diseases, Department of Public Health and Preventive Medicine, Oregon Health & Science University; Professor of Epidemiology Programs, Oregon Health & Science University and Portland State University School of Public Health, Portland, Oregon
Mycobacterium avium *Complex*

Karen K. Wong, MD, MPH
Medical Officer, Division of Foodborne, Waterborne, and Environmental Diseases, Centers for Diseases Control and Prevention, Atlanta, Georgia
Foodborne Disease

Glenn W. Wortmann, MD
Section Director, Infectious Diseases Service, MedStar Washington Hospital Center, Washington, DC; Professor of Medicine, Infectious Diseases, Uniformed Services University of the Health Sciences F. Edward Hebert School of Medicine, Bethesda, Maryland
Drugs for Protozoal Infections Other Than Malaria

William F. Wright, DO, MPH
Division of Infectious Diseases, Department of Medicine, University of Pittsburgh Medical Center, Pinnacle, Harrisburg, Pennsylvania
Fever of Unknown Origin

David L. Wyles, MD
Chief, Division of Infectious Diseases, Department of Medicine, Denver Health Medical Center, Denver, Colorado; Professor of Medicine, University of Colorado School of Medicine, Aurora, Colorado
Hepatitis C

Jo-Anne H. Young, MD
Professor of Medicine, University of Minnesota, Minneapolis, Minnesota; Editor-in-Chief, Clinical Microbiology Reviews, American Society of Microbiology, Washington, DC; Associate Editor, Biology of Blood and Marrow Transplantation, American Society for Transplantation and Cellular Therapy, Chicago, Illinois
Infections in Recipients of Hematopoietic Stem Cell Transplants

Vincent Bensan Young, MD, PhD
William Henry Fitzbutler Collegiate Professor, Department of Internal Medicine, Division of Infectious Diseases, University of Michigan Medical School, Ann Arbor, Michigan
Clostridioides difficile (*Formerly* Clostridium difficile) *Infection*

Nadezhda Yun, MD
Assistant Professor, Department of Pathology, Scientific Manager, Preclinical Studies Core
Galveston National Laboratory, University of Texas Medical Branch, Galveston, Texas
Lymphocytic Choriomeningitis Virus, Lassa Virus, and the South American Hemorrhagic Fevers (Arenaviruses)

Werner Zimmerli, MD
Professor, Basel University; Interdisciplinary Unit of Orthopaedic Infection, Kantonsspital Baselland, Liestal, Switzerland
Orthopedic Implant–Associated Infections

Stephen H. Zinner, MD
Charles S Davidson Distinguished Professor of Medicine, Harvard Medical School, Boston, Massachusetts; Past Chair, Department of Medicine, Mount Auburn Hospital, Cambridge, Massachusetts
Sulfonamides and Trimethoprim; Trimethoprim-Sulfamethoxazole

John J. Zurlo, MD
The W. Paul and Ida Havens Professorship of Infectious Diseases, Director, Division of Infectious Diseases, Thomas Jefferson University, Philadelphia, Pennsylvania
Pasteurella *Species*

Preface to the 9th Edition

The field of infectious diseases continues its extraordinary expansion of knowledge. Now in its 9th edition, *Principles and Practice of Infectious Diseases* remains dedicated to a clear, complete, up-to-date, and—most importantly—authoritative presentation of the current information. In the last edition we included online updates to keep the text current, and we are planning for this in the 9th edition as well.

In the 9th edition and in clinical practice, previously rare or remote infectious diseases such as Zika, Ebola, and hepatitis E viral infections compete for attention with new drugs and diagnostic tests. Details and rationales are provided for new treatments for many infections, including hepatitis C, human immunodeficiency virus (HIV), tuberculosis, methicillin-resistant *Staphylococcus aureus* (MRSA), and *Clostridioides (Clostridium) difficile,* as well as treatment options for increasingly antibiotic-resistant bacteria. Awareness of infections imported from overseas on food, travelers, exotic pets, and immigrants has become even more imperative as the world gets smaller. The complexities of managing infections in patients immunosuppressed by new drugs and by stem cell or organ transplantation requires extensive updating, as well as issues arising in patients with implanted mechanical hearts or prosthetic joints. Improved diagnostic tests for *C. difficile*, respiratory and enteric pathogens, *Tropheryma whipplei*, and many other organisms are now broadly available. In addition, there have been continuing advances in understanding of the human microbiome and in its relationships with both health and disease, and of molecular microbiology, pathogenesis, and host responses; all of these are addressed as well. As before, *Principles and Practice of Infectious Diseases* is divided into relevant sections that cover all of these areas and that are presented in an interrelated manner. Based on our custom, we focus on individual pathogens as well as on important clinical syndromes. This broadens the context to consider complex information in the setting of ill patients. We believe this provides tools for both the advanced practitioner and the beginner to understand and treat infectious diseases.

The authors who have been selected to write each of the individual chapters in the book are recognized experts in their fields, and, in turn, every chapter is carefully reviewed by all three editors to be placed into appropriate context and perspective. Thus, we anticipate that *Principles and Practices of Infectious Diseases* will be of interest and use to a wide audience of physicians, including infectious disease clinicians, internists, family practitioners, and HIV/AIDS specialists, as well as to health care providers in all other areas of medicine, public health experts, microbiologists, immunologists, hospital infection control specialists, and other medical scientists.

The editors and publisher of *Principles and Practice of Infectious Diseases* have gone to great effort to ensure that its content is highly accessible and current. The text, figures, and tables are readily available through Expert Consult, which is accessible through a powerful and easy-to-use search engine and is compatible with PC, Mac, most mobile devices, and eReaders. In addition, chapters have an introductory short summary, which is linked to individual content in each chapter. Individual chapters will also be updated on a regular basis to ensure that their content remains current. The appropriateness and significance of the updates will be emphasized by the authors and editors.

The 9th edition of *Principles and Practice and Infectious Diseases* represents the extraordinary efforts of many individuals. Foremost are the contributions of authors of the 323 individual chapters, who are dedicated to maintaining the tradition of an authoritative text that meets the highest standards of accuracy and integrity. Drs. Mark Parta, Yehuda Cohen, and Henry Redel served as assistant editors in the 8th edition and provide important assistance in the update program.

We are very grateful to Judy Webber, Janet Morgan, and Dr. Paola Frattaroli for the invaluable assistance that they have provided to us. We would also like to thank Lucia Gunzel, Taylor Ball, Lotta Kryhl, Dolores Meloni, and Kristine Feeherty at Elsevier for their overall support and efforts. And as always, this work would not have been possible without the encouragement, understanding, and—as needed—forbearance of our wives, Shirley Bennett, Kelly Dolin, and Maria Gloria Dominguez Bello.

JOHN E. BENNETT, MD
RAPHAEL DOLIN, MD
MARTIN J. BLASER, MD

Basic Principles in the Diagnosis and Management of Infectious Diseases

I

A Microbial Pathogenesis

1

A Molecular Perspective of Microbial Pathogenicity

David A. Relman,[a] Stanley Falkow,[†] and Lalita Ramakrishnan

Humans evolved on a planet dominated by microbes, which are mind-boggling in number and diversity, and thus have been intimately associated with them since the beginning. Host-associated microbes typically derive or provide benefits from this association and are thus called "commensals," which literally means "those that eat at the same table" (for definitions of classes of host-associated microbes, see Table 1.1). When they both give and receive benefits, the microbes are called "mutualists." Practically speaking, it is difficult to know whether a specific microbe is a commensal or a mutualist (or neither) because its role in the ecosystem may be subtle and its impact indirect via its relationships with other community members. In the environment, microorganisms live almost exclusively in complex communities with strong interactions among members, both cooperative and competitive, and dependencies as well as evidence of adaptation to their habitat. Not surprisingly, human commensals likewise live in complex communities; these communities are referred to as the human microbiota and, together with their genes, the human microbiome.[1,2] The number of microbial cells associated with the human body rivals the total number of human cells,[3] and the number of unique genes and gene functions associated with the human microbiome exceeds by at least 100-fold the number of unique human genes.

Host-microbiota associations are host-species specific. For example, the mouse gut microbiota is much more effective than the human or even the rat microbiota in driving differentiation of the murine immune system when used to colonize a germ-free mouse.[4] Variation in gut microbiota structure of terrestrial animals is only partly explained by host genetic relatedness; diet and gut anatomy, that is, whether fermentation takes place in the foregut or the hindgut, also explain some of this variation. More intriguing, the structure and function of human and other animal microbiotas exhibit distinct nonrandom patterns across body sites and, with time, across early life, weaning, puberty, and other life-stage transitions. The human microbiota confers a wide array of critical benefits upon its host, including nutrient and micronutrient (e.g., vitamin) availability and energy extraction from food; terminal postnatal differentiation of mucosal structures, such as the epithelial brush border and barrier function; immune system development; regulation of intermediary metabolism; processing of ingested chemicals; and "colonization resistance" against pathogens.[5] In turn, humans provide benefits to their microbiota, such as nutrients and growth factors, protected habitat, and the means for dispersal. It is important to note that this mutualistic relationship of the microbiota with the host does not necessarily mean that all individual members are also mutualists. Some may just be commensals, where they receive benefits from the host and are neither helpful nor harmful.

What then is a pathogenic microorganism? From an infectious diseases viewpoint, any microorganism that is capable of causing disease is a pathogen (see Table 1.1). Microbes that are pathogenic for humans are subsumed within the domains Bacteria and Eukarya but are restricted to the relatively few phyla that contain human-adapted members. Controversy surrounds the possible classification of some archaea as pathogens[6] (see later). As in previous editions, we will focus in this chapter on pathogenic bacteria, which are the best studied. The lessons gleaned from the study of the mechanisms by which bacteria cause disease are broadly generalizable to the less well-understood protozoa, helminths, and fungi. Viral pathogenesis mechanisms, many of which are understood in exquisite detail, are discussed in Chapter 131 and in the individual chapters on specific viruses. What is becoming increasingly clear is that there is considerable overlap in the pathogenic mechanisms of bacteria and viruses and in the host responses to them.

To be called a pathogen, a microorganism does not always have to cause disease; many common and serious infectious diseases in immunocompetent hosts are caused by organisms typically found within the human microbiota, competing with other indigenous microbes and for the most part adopting a commensal lifestyle (see Table 1.1). However, disease caused by these so-called commensal pathogens is almost certainly an accident because disease is not required for their evolutionary survival. In contrast, obligate pathogens depend on disease causation for transmission and thereby evolutionary survival (see Table 1.1), although they too can cause asymptomatic infection. A good example is *Mycobacterium tuberculosis*. The incubation period (i.e., the time from acquisition of the organism to overt disease) of tuberculosis (TB) is usually between weeks and months, although occasionally *M. tuberculosis* can cause asymptomatic infection for years.[7] Yet, *M. tuberculosis* is only transmitted through aerosol infection when diseased patients cough; asymptomatically infected individuals do not transmit infection. In

[a]All material in this chapter is in the public domain, with the exception of any borrowed figures or tables.
[†]Deceased.

TABLE 1.1 Types of Microbes That Establish Relationships With Humans

Commensal	A microorganism that is a normal inhabitant of the human body. In commensal relationships, either the microbe or host derives benefit; neither is harmed. In mutualistic relationships, such as with *Lactobacillus crispatus*, both derive benefit.	*Faecalibacterium prausnitzii* *Ruminococcus bromii* *Bacteroides ovatus* *Akkermansia muciniphila* *Streptococcus sanguinis* *Lactobacillus crispatus*
Pathogen	A microorganism capable of causing disease. These include commensals and noncommensals. Operational classes of pathogen are defined in the rows below.	
Obligate pathogen	A microorganism that must produce disease to transmit and thereby survive evolutionarily. Obligate pathogens are not commensals, although they can produce asymptomatic infection.	*Mycobacterium tuberculosis* *Mycobacterium leprae* *Treponema pallidum* *Neisseria gonorrhoeae* *Shigella dysenteriae* *Salmonella* Typhi *Chlamydia trachomatis*
Commensal pathogen	A microorganism that is commonly found within the indigenous microbiota that can cause disease in normal hosts with some regularity. Commensals do not manifest as pathogens with equal frequency; *Bacteroides fragilis* and *Streptococcus anginosus* are occasional rather than regular pathogens, in contrast to the others on the list. Disease causation is not required for the commensal's survival and as such is an accident.	*Staphylococcus aureus* *Streptococcus pyogenes* *Streptococcus pneumoniae* *Neisseria meningitidis* *Haemophilus influenzae* *Helicobacter pylori* *B. fragilis* *S. anginosus*
Zoonotic pathogen	A microorganism that is a colonizer or pathogen in animals and that can be transmitted to humans either via an insect vector or via direct contact with the animal or its products. Disease causation in humans is accidental and not necessary for evolutionary survival.	*Yersinia pestis* *Francisella tularensis* *Borrelia burgdorferi* *Bacillus anthracis* *Brucella abortus* *Mycobacterium bovis* *Mycobacterium leprae* *Salmonella enterica* *Rickettsia spp.*
Environmental pathogen	A microorganism capable of causing disease that is transmitted to humans from an environmental source such as water or soil. Disease causation is accidental and not necessary for evolutionary survival.	*Clostridium tetani* *Clostridium botulinum* *Burkholderia pseudomallei* *Mycobacterium marinum* *Mycobacterium avium* *Pseudomonas aeruginosa* *Legionella pneumophila* *Vibrio cholerae*

the case of *Salmonella* Typhi another obligate pathogen, individuals can occasionally remain persistently, although asymptomatically infected after a bout of typhoid fever, and unlike the case of TB, these asymptomatically infected individuals can shed the organisms in their feces, as notoriously exemplified by "Typhoid Mary." However, the vast majority of transmission likely occurs through diseased patients; it is disease rather than asymptomatic shedding by a minority population that sustains the global burden of typhoid fever.

The remaining two classes of disease-causing microbes are zoonotic and environmental pathogens, where infection of humans originates from other animals and the environment, respectively (see Table 1.1). As with commensal pathogens, human disease from zoonotic and environmental pathogens is accidental and does not benefit the pathogen's survival. It is important to note that pathogens of all classes can cause very serious disease. Humanity's greatest infectious killers include not only tuberculosis, caused by an obligate pathogen, but also group A streptococcal disease, plague, and cholera, caused respectively by a commensal, a zoonotic, and an environmental pathogen. Thus countless millions have succumbed and continue to succumb to bacterial diseases that are of no benefit to the causative agent.

This classification of pathogens is not absolute because they continue to evolve and adapt at the same time as their hosts change in behavior and demographics. *Mycobacterium leprae* is a good example of a pathogen with dual pathogen class membership. A scourge of humankind for millennia, *M. leprae* was likely once a strictly obligate human pathogen (i.e., completely reliant on human-to-human transmission for its evolutionary survival). However, Hansen disease (leprosy) represents an instance of a "reverse zoonosis" on at least two different occasions. Humans infected red squirrels in the British Isles in medieval times, when there was likely close contact with squirrels owing to a squirrel fur trade, and because red squirrels were able to infect each other, they have leprosy to this day.[8] Then approximately 400 years ago, after *M. leprae* was brought into the new world through the slave trade, armadillos in the southeastern United States became infected, again probably through close human contact.[9] Leprosy is spreading among armadillos and from armadillos to humans and is now a recognized zoonotic disease in the United States.

Pathogens are not equally virulent (i.e., they do not have an equal probability of causing disease). For example, encapsulated pneumococci are more virulent than nonencapsulated pneumococci, and *Escherichia coli* strains that express Shiga-like toxins are more virulent than those that do not express these toxins. Thus it is useful to distinguish pathogens that regularly cause disease in some proportion of susceptible individuals with apparently intact defense systems ("primary pathogen") from others that cause disease only in immunocompromised individuals ("opportunistic pathogen"). A distinction, then, between a primary pathogen and opportunist is that the former has an *inherent* ability to breach the host barriers that ordinarily restrict other microbes, whereas the opportunist requires some underlying defect or alteration in the host's defenses, whether it be genetic, iatrogenic, ecologic (altered microbiota), or caused by underlying disease or trauma, to establish itself in a usually privileged host niche. However, the distinction is often not clear-cut because a primary pathogen is often opportunistic as well. *Streptococcus pneumoniae* can cause disease in apparently immunocompetent hosts, but individuals with asplenia or human immunodeficiency virus (HIV) infection are even more susceptible to it. *Neisseria meningitidis* is a dreaded primary pathogen to which individuals with terminal complement deficiencies are more likely to develop disease. *M. tuberculosis*, a major cause of disease and death in immunocompetent individuals, poses a higher risk for individuals with HIV infection.

The distinction between primary and opportunistic pathogen is actually even muddier, as illustrated by the case of *Pseudomonas aeruginosa* infections. *P. aeruginosa* is generally viewed as an opportunistic pathogen because it does not usually cause disease in individuals with intact host defense systems and is a more common cause of lethal pneumonia and bacteremia in neutropenic hosts. But even in normal hosts, *P. aeruginosa* can cause benign self-limited skin eruptions ("hot tub" folliculitis) in individuals exposed to contaminated water in hot tubs. Moreover, *P. aeruginosa* illustrates the point that pathogenicity can only be understood in the context of a specific host. In individuals with cystic fibrosis, *P. aeruginosa* produces a lung-destroying chronic bronchitis, but unlike the case with pneumonias in neutropenic hosts, the organism does not disseminate systemically, so overt bacteremia is not usually associated with the lung infection. In elderly patients with diabetes mellitus, *P. aeruginosa* can produce a completely different devastating disease—malignant (necrotizing) otitis externa, an invasive infection of the external auditory canal and bones of the skull base. In general the stereotypic patterns of infection by primary and opportunistic pathogens in distinct disorders of host defense provide useful clues for early diagnosis and treatment and about pathogenic mechanisms.

An emerging concept of microbial disease causation, with origins in the field of ecology, is the notion of "community as pathogen."[1] This notion is based on the idea that community members, incapable of causing disease on their own, together cause pathology through the kinds of cooperative interactions that are typical of all microbial communities, such as cross-feeding (one member secretes a factor that serves

as a nutrient for another member), syntrophy (see later), or cross-protection (one member secretes a factor that protects another member from a harmful environmental compound). Examples of such "pathogenic communities" have been studied in mouse models where microbial communities that arise only in mice with a dysregulated immune system are then capable of transmitting a form of ulcerative colitis to wild-type mice.[10] In humans "pathogenic communities" in the mouth are associated with chronic periodontitis.[11] Indeed, it is in the context of pathogenic communities that archaea have been implicated in human infectious disease causation.[11–13] For example, methanogens in the subgingival crevice may enhance the growth of fermentative, "nascent" pathogenic bacteria, and benefit themselves by consuming the hydrogen produced by the fermenters in a relationship called "syntrophy." Other hydrogen-consuming microbes, such as treponemes, may take the place of the archaeal methanogens in these communities. The concept of a pathogenic community poses special challenges for proofs of causation because the pathogenic "agent" is difficult to isolate, purify, and characterize, and relevant models of disease can be elusive. Dominant ideas of microbial disease causation (e.g., a single pathogenic agent in a susceptible host) may be too restrictive. Moreover, microbial diseases that require or support a consortium of microbes (e.g., intraabdominal abscess), pose challenges for pathogen identification.

Discussions about pathogenic communities have been grounded in traditional ecologic definitions of the term community that specify multiple interacting species with networked interspecies relationships. Yet, local populations of bacteria from the same species, even clonal diversified descendants of a single cell, can also be viewed as communities because of the seemingly cooperative behavior of diversified and heterogenous subpopulations. And this alternative view has provided important insights into the strategies, that is, "social behavior," of some pathogens.[14] For instance, clonal populations of pathogens can vary in their expression of genes. As one example, within a population of *Salmonella typhimurium* cells growing in axenic culture, there are subpopulations that express a virulence-associated specialized secretion system that facilitates invasion of intestinal epithelial cells. This preemptive expression of a virulence factor represents a form of "bet-hedging" to prepare the bacterium for a variety of different, changing local conditions and needs. Heterogeneity in gene expression is also seen in subpopulations of bacteria that have encountered different environmental conditions within the host and presumably responded accordingly. *Salmonella* attracts both macrophages and neutrophils to the intestinal mucosa; not surprising, bacteria phagocytosed by these two cell types express different genes even within the same inflamed tissue. Even extracellular bacteria close to each other might express distinct genes in response to local differences in oxygen tension or pH within an abscess.

Finally, populations of pathogens may display heterogeneity because of the emergence of "cheaters." Again, *S. typhimurium* provides a good example. Its specialized secretion system that facilitates invasion of intestinal epithelial cells also elicits a host inflammatory response that is favorable to itself and to a small select number of distant relatives (other members of *Enterobacteriaceae*) but not to the vast majority of commensal competitors. Because the secretion system is costly to make, cheaters arise that can benefit from the inflammation caused by their siblings without undergoing the cost of making the secretion system.[15] However, if cheaters become too numerous, then there will not be sufficient inflammation, and the entire population will be disadvantaged. Therefore there have evolved intrinsic measures to keep the number of cheaters in check, and in fact, bacteria are known to have "cheater detection" mechanisms!

ATTRIBUTES OF MICROBIAL PATHOGENS

Despite the difficulties in defining them, pathogens do share characteristic attributes (Table 1.2). All pathogens (other than commensal pathogens) must gain entry into the host in sufficient numbers to establish infection, either from another infected host, the environment, or an insect vector. All classes of pathogens must be able to establish themselves in a unique habitat; this typically occurs by breaching anatomic barriers to "go where other microbes dare not." Another important trait of a pathogen is replication within its host; disease production is usually dependent on this trait, as is transmission, an essential trait of obligate pathogens. These discrete steps are achieved by avoiding, circumventing, destroying, or even exploiting one or more essential host defenses. The degree to which a microbe can subvert to their advantage the cellular processes in a normal host not only distinguishes commensals from pathogens,[16,17] but also among commensals, organisms that have greater or less propensity to cause disease (see Table 1.1).

TABLE 1.2 Attributes Shared by Bacterial Pathogens

- Enter host. This can occur through the skin or any of the body's orifices. Commensal pathogens bypass this step as they are "already there."
- Cross anatomic barriers and/or breach other host defenses to establish themselves in a unique habitat and functional niche.
- Multiply within host.
- Exit from the host to infect new host. Only obligate pathogens need to do this.

Modified from Falkow S. I never met a microbe I didn't like. Nat Med. *2008;14:1053–1057.*

For the steps of pathogenesis to be executed, the microorganism must possess genetic properties, often complementary and coregulated, that promote its interaction with the human host. Commensal organisms also rely on their genetic properties to maintain their interactions with the host and with other community members. Indeed, the genetic traits of a given microorganism define the unique attributes that enable it to follow a common sequence of steps to establish colonization or disease.[18,19] Elegant molecular and genetic techniques have enabled the identification, isolation, and characterization of many of these genes and their products (see "Identification and Characterization of Virulence Genes"). We now also possess the complete genome sequences of virtually every major pathogenic bacterial species. This information provides important clues and insight into the potential of a microorganism for causing disease and facilitates new experimental strategies for understanding pathogens and commensals alike.[20,21]

These methods, information, and insights have led to the identification of *virulence factors*, the properties (e.g., gene products) that enable a microorganism to achieve its pathogenic potential through these steps; from a clinician's point of view, a virulence factor enhances the microbe's potential to cause overt pathology. The critical need for virulence determinants is obvious when one considers that the execution of the steps of pathogenesis (or, for that matter, colonization) in the face of a formidable array of host defense mechanisms is nontrivial. The availability of the host (e.g., human) genome sequence has significantly enhanced our understanding of the mechanisms of host defense and pathogen counterdefense,[22] while enabling multiple synergistic approaches for understanding virulence, including the identification of host susceptibility traits and genome-wide assessments of host response. It is becoming clear that pathogens possess specific determinants mediating virulence, distinct from those enabling general metabolic functions, that imbue them with a counterstrategy for each host defensive strategy.

The initial steps of entry and niche establishment require that the microorganism make contact with an appropriate host tissue that can serve as a jumping board to its eventual host niche. To accomplish this goal the infecting microbe may make use of motility (through *flagella*), chemotactic properties, and adhesive structures (or *adhesins,* such as *pili*) that mediate binding to specific eukaryotic cell receptors or to other microorganisms.[16,23] They must adapt, at least temporarily, to the particular nutrient environment in which they find themselves. They must resist host antimicrobial peptides and avoid phagocytosis and killing by patrolling innate immune cells of the host. They must contend with the indigenous microbiota that provides competition against establishment of the newcomer.

Because breaching barriers is generally an integral aspect of reaching their preferred site for replication, most pathogens have specific virulence determinants that enable them to do this. These barriers can be anatomic, cellular, or biochemical and may prevent entry by other microorganisms into what are ordinarily sterile tissue sites. Breaching these diverse types of barriers requires pathogens to elaborate toxins and enzymes that

destroy anatomic barriers while countering innate immune defenses by either avoiding phagocytosis, for instance, by means of an antiphagocytic capsule, or by simply killing phagocytes. Paradoxically, many intracellular pathogens (e.g., *Salmonella* and *Mycobacterium*), rather than breaching anatomic barriers, typically *use* phagocytes to ferry them across these barriers, and others (e.g., *Listeria*, *Rickettsia*, and *Shigella*), spread from one nonphagocytic cell to the next by co-opting the host cell actin assembly machinery.[24]

In most infectious diseases, save those few that involve a preformed toxin, the infecting organism must multiply to produce disease. This can be appreciated in clinical practice in terms of a characteristic incubation period spanning the time from exposure to the appearance of signs and symptoms of disease. The diversity of pathogen habitats—extracellular or intracellular, mucosal or submucosal, within the bloodstream or within another privileged anatomic site—has forced pathogens to evolve distinct biochemical tactics to achieve this goal. Intracellular pathogens have to ward off the defenses of the host cell, which in the case of professional phagocytes, such as macrophages and neutrophils, are geared toward killing microbes.

Finally, obligate pathogens have evolved diverse strategies to exit the host that serve to increase transmission to a new host. *Shigella dysenteriae* and *Neisseria gonorrhoeae* both elicit neutrophil-dominated mucosal inflammatory responses that lead to diarrhea and exudates, respectively, laden with organisms, that facilitate bacterial exit and transmission to new hosts either via the environment or directly. *M. tuberculosis* orchestrates the necrotic death of infected macrophages in the tuberculous granuloma, a process that enhances transmission.[25]

Microorganisms also use subtle biochemical mechanisms to avoid, subvert, or, as we now increasingly understand, manipulate host defenses. These strategies include the elaboration of immunoglobulin-specific proteases, iron sequestration mechanisms, coating themselves with host proteins to confuse the immune surveillance system or causing host cells to signal inappropriately, leading to dysregulation of host defenses or host cell death. Examples of these mechanisms include the production of immunoglobulin A1 protease by meningococci, the use of receptors for iron-saturated human transferrin and lactoferrin by gonococci, and the coating of *Treponema pallidum* with human soluble fibronectin. Antigenic variation and intracellular invasion are other common strategies used by successful pathogens to avoid immune-mediated elimination.[17,26] The broad principle is that for any host defense strategy, a successful pathogen must have evolved a counterstrategy.

Any discussion of virulence factors, and particularly their link to specific virulence functions, begs the question as to whether, how many, and which commensal organisms can also act as primary pathogens. The well-known virulence factors of commensal pathogens, many of which reside in the mucosa of the nasopharynx can be thought of as colonization factors run amok. These factors likely evolved to give the commensal a selective colonization advantage on mucosal surfaces rife with microbial competition. They might also help to maintain an equilibrium with host defenses. In support of this idea, vaccines against virulence factors often eradicate colonization along with disease. This is true for vaccines against bacterial capsules, for instance, those of *S. pneumoniae* and *N. meningitidis*, demonstrating that the capsules of these bacteria enable effective colonization.

Pathogenic bacteria have evolved sophisticated biochemical strategies to interfere with, or manipulate for their own benefit, the normal function(s) of host cells, but their "purpose" is not to "do in" their host! Rather, from a teleologic perspective, the diseases they cause are simply a by-product of the method and site chosen by (or thrust upon) them for replication and evolutionary persistence. In fact, disease per se is not a measure of microbial success—in evolutionary terms, a prevalent human commensal is just as successful as a prevalent human pathogen, such as *M. tuberculosis*, one of humanity's greatest killers. Although death of a host may promote transmission of some infections, it is more often detrimental to both parties involved. Therefore the rules of host-pathogen engagement, certainly for obligate pathogens, are generally designed to produce a tie: just enough pathogen multiplication and damage to the host to ensure its establishment within that host and transmission to a new host, but no more than is tolerated by the host. It is true that some of the most notorious infectious diseases (e.g., plague) occur predominantly in dramatic epidemic form; indeed, the so-called "emerging" infectious diseases reflect various aspects of imbalance in the relationships among host, pathogen, and environment.[27] However, most of these diseases are the result of accidental infection by zoonotic pathogens.[28] In most zoonotic diseases the rules of host-pathogen engagement are blurred, often to the detriment of both host and microbe, serving as an evolutionary dead end for both parties.

Finally, in framing the question "What is a pathogen?" it is important to consider that we yet do not know the true diversity and distribution of extant microorganisms capable of causing human disease. Previously unrecognized pathogens emerge with increasing frequency, and although most are zoonotic, the accelerated clip of pathogen discovery does highlight the uncertainty about how often, in what phylogenetic backgrounds, and through what mechanisms virulence for humans among microbes can arise. It is highly likely that some potential pathogens may not have had adequate contact with humans to have made themselves known yet.[29] Although pathogen detection and identification remain suboptimal, in part because of continuing dependence on cultivation methods and targeted species-specific assays that fail to detect novel pathogens,[30] it is also the case that pathogens-in-waiting are the beneficiaries of human activities that alter the climate and landscape, create crowded living conditions, and impede sanitation and other public health measures through strife and the withholding of needed resources.

EVOLUTION OF BACTERIAL PATHOGENICITY

Where do pathogens come from? The quest to understand how pathogenic bacteria cause disease dates back well more than a century. The notion that bacteria somehow "poison" host cells predates even the isolation of individual pathogens, a concept that was solidified with the demonstration in 1888 and 1890, respectively, that culture filtrates from *Corynebacterium diphtheriae* and *Clostridium tetani* were sufficient to cause their respective diseases in experimental animals. Since then, hundreds of bacterial toxins have been discovered and their mechanisms of action discerned. Other bacterial virulence factors (e.g., adhesins, capsules) have been identified as well, and a sophisticated understanding of their mechanisms achieved. But how did bacteria *become* pathogens, or in other words, how did they acquire these armaments? It turns out that virulence determinants such as toxins and adhesins, that distinguish pathogens from their nonpathogenic relatives, derive from specialized genes possessed by pathogens but absent in nonpathogens. These specialized genes reside on DNA that often is foreign to the bacteria, either as part of extrachromosomal plasmids, transposons ("jumping genes"), or bacterial viruses (bacteriophages) integrated into the bacterial chromosome (Table 1.3).

Virulence gene discovery (see "Identification and Characterization of Virulence Factors"), which was accomplished for decades by genetic and biochemical methods, has been greatly accelerated in recent years by the feasibility of large-scale whole-genome sequencing and genome-wide single nucleotide polymorphism analysis.[20] Since the first description of a complete genome sequence for a free-living organism, *Haemophilus influenzae,* in 1995,[31] more than 180,000 bacterial and archaeal complete genome sequences have been released to public databases (www.ncbi.nlm.nih.gov/genome/browse/). Comparative genome analyses suggest that the inheritance of pathogenic traits was not the result of slow adaptation to the host but rather a rapid acquisition of genes *en bloc* via mobile genetic elements (i.e., plasmids, transposons, phages). Consistent with their acquisition on mobile elements, these virulence-associated sequences are often bounded by repeated DNA segments, which are a signature of mobile DNAs. Moreover, inspection of genome sequences finds that these virulence determinants and their associated (residual) mobile elements often have a distinct genome nucleotide composition, suggesting that their ancestry derives from an unrelated microbe.

This duality of chromosomal nucleotide composition in pathogenic bacteria is most apparent in the context of *pathogenicity islands*, large blocks of genes that some pathogens have acquired through genetic transfer from other bacteria.[32] These islands comprise clusters of virulence-associated genes that encode specialized secretion systems

TABLE 1.3 Examples of Plasmid- and Phage-Encoded Virulence Determinants

ORGANISM	VIRULENCE FACTOR	BIOLOGIC FUNCTION
Plasmid Encoded		
Enterotoxigenic *Escherichia coli*	Heat-labile, heat-stable enterotoxins	Activation of adenylate/guanylate cyclase in the small bowel, which leads to diarrhea
	CFA/I and CFA/II	Adherence/colonization factors
Extraintestinal *E. coli*	Hemolysin	Cytotoxin
Shigella spp. and enteroinvasive *E. coli*	Gene products involved in invasion	Induces internalization by intestinal epithelial cells
Yersinia spp.	Adherence factors and gene products involved in invasion	Attachment/invasion
Bacillus anthracis	Edema factor, lethal factor, and protective antigen	Edema factor has adenylate cyclase activity; lethal factor is a metalloprotease that acts on host signaling molecules
Staphylococcus aureus	Exfoliative toxin	Causes toxic epidermal necrolysis
Clostridium tetani	Tetanus neurotoxin	Blocks the release of inhibitory neurotransmitter, which leads to muscle spasms
Phage Encoded		
Corynebacterium diphtheriae	Diphtheria toxin	Inhibition of eukaryotic protein synthesis
Streptococcus pyogenes	Erythrogenic toxin	Rash of scarlet fever
Clostridium botulinum	Botulism neurotoxin	Blocks synaptic acetylcholine release, which leads to flaccid paralysis
Enterohemorrhagic *E. coli*	Shiga-like toxin	Inhibition of eukaryotic protein synthesis
Vibrio cholerae	Cholera toxin	Stimulates adenylate cyclase in host cells

CFA, Colonization factor antigen.
Data from Elwell LP, Shipley PL. Plasmid-mediated factors associated with virulence of bacteria to animals. Annu Rev Microbiol. *1980;34:465–496; and Cheetham BR, Katz ME. A role for bacteriophages in the evolution and transfer of bacterial virulence determinants.* Mol Microbiol. *1995;18:201–208.*

and secreted effector molecules that provide the microbe with extraordinary properties to survive in a specific host, such as adhesins and proteins that regulate virulence gene expression (see "Regulation of Bacterial Pathogenicity" and "Close Encounters: Pathogens as Cell Biologists"). *S. typhimurium* is believed to have begun evolving as a pathogen from a common ancestor that it shares with *E. coli,* approximately 130 million years ago, through the sequential acquisition of at least two pathogenicity islands, one of which mediates internalization within host cells, and the other, survival and replication within an intracellular vacuole. Although genomic analyses provide us with fascinating stories about the evolution of pathogens, we still remain ignorant of the precise origins of these and other virulence-associated systems. They were probably acquired from a yet unknown ancient ancestor. Moreover, it seems likely that their acquisition by pathogens can be traced to their need for avoiding predation as more sophisticated organisms evolved, such as free-living amebae, nematodes, fungi, and a host of other tiny creatures that exploit microbes for food. Pathogenicity is an old and honorable bacterial trait!

Hence we can conclude that, in most cases, bacteria have evolved to become pathogens by *acquiring* genetic material encoding virulence determinants rather than by the gradual loss of genes. This is not to say that, over time, some pathogens do not dispense with genes that are no longer useful for their newly acquired pathogenic lifestyle. Indeed, gene loss or gene inactivation is often associated with the adaptation of a pathogen to a particular host. Continuing our genomic "stalking" of *Salmonella*, we find that *S. typhi,* the strictly human-adapted bacterium that causes typhoid fever, has acquired by horizontal gene transfer (HGT) a unique capsular polysaccharide, Vi, and a unique toxin not present in *S. typhimurium*.[33] Yet it has also lost or inactivated a large number of genes present in *S. typhimurium*.

Shigella and *Yersinia* provide other examples of evolution to pathogenicity through both acquisition and loss of genes. The different pathogenic *Shigella* spp. are believed to have arisen on several independent occasions from within different *E. coli* lineages, and in the case of *Shigella sonnei*, the emergence of the species occurred quite recently (i.e., only 400 years ago). The *Shigella* spp. arose through convergent evolution, with acquisition of a virulence plasmid carrying genes for invasion and manipulation of host cells and a bacteriophage carrying the Shiga toxin gene, along with loss of genes for flagella that were not only unnecessary in light of the new armaments that each species had acquired but even detrimental because the immunogenicity of flagella would provoke a host response that would promote elimination of the bacteria.[34]

The case of *Yersinia pestis* provides perhaps the most fantastic example of hand-in-hand gene acquisition and loss. It is estimated that *Y. pestis* evolved from the enteropathogenic *Yersinia pseudotuberculosis* only approximately 5000 years ago.[35] All pathogenic *Yersinia* spp. harbor a 70-kilobase virulence plasmid (pYV) needed for toxicity and to overcome host immune defenses, but there are two *Y. pestis*–specific plasmids that were more recently acquired by HGT. One encodes a plasminogen activator, a surface molecule that provides proteolytic, adhesive, and invasive functions and facilitates dissemination from an intradermal site of infection. The other plasmid encodes a capsular antigen that blocks phagocytosis and a toxin needed for survival in the flea. Thus this organism evolved to establish a distinct mammalian reservoir, ensure its transmission by a flea, and spread systemically in its preferred murine host, with obvious devastating effect in an accidental human host. In the process it rearranged its genome and inactivated genes that were required for its previous gastrointestinal life; these inactivated genes and rearrangements remain as evolutionary relics. That a microorganism can accomplish this remarkable feat of evolution in what is a blink of the eye in evolutionary terms, may be a cautionary lesson for what the future may hold for emerging pathogens.

In general, as bacteria evolve from free-living organisms with multiple habitats to obligate pathogens, host-restricted organisms, endosymbionts, or obligate intracellular organisms, their genomes become reduced in size, accumulate inactive or defective genes *(pseudogenes),* or both.[20,36] For example, the evolution of *Bordetella pertussis* as a host-specific, human-adapted pathogen from a *Bordetella bronchiseptica*–like ancestor has been accompanied by extensive gene loss and gene inactivation (3816 coding sequences vs. 5007 for *B. bronchiseptica*; 9.4% of coding sequences are pseudogenes vs. 0.4% for *B. bronchiseptica*).[37] In this case, a highly restricted host range (*B. pertussis* is a strictly human pathogen) has meant loss of genetic diversity. In contrast to *B. bronchiseptica*, which infects multiple animal hosts and can survive in the environment, *B. pertussis* varies little in gene content among different strains isolated over the past 50 years and across several continents.[38] However, more recent analyses of whole-genome sequence assemblies and gene order have revealed clone-specific genome structural rearrangements and have led to speculation that certain genome rearrangements may confer fitness benefits and differences in virulence.[39] *M. tuberculosis*, a human-adapted pathogen, has a significantly smaller genome than its soil-dwelling relative *Mycobacterium smegmatis*. *M. leprae*, the agent of leprosy, is so exquisitely host adapted that it cannot even be grown in axenic culture, and in accordance, its genome displays an extreme degree of gene decay. Overall, the primary evolutionary push to pathogenicity results from gene acquisition. More generally, gene acquisition is an effective strategy for microbial specialization and a means for haploid organisms to acquire new functions and maximize diversity while fulfilling their need to conserve essential functions. The gene loss that occurs alongside gene acquisition makes the organism more efficient in one environment yet

may make it more limited in others, *M. leprae* being an extreme example of evolving to a restricted niche.

One revelation from pathogen "genome gazing" is that the amount of acquired DNA associated with virulence and adaptation to a host habitat varies greatly between bacterial pathogens. In pathogenic *E. coli* strains this amount is substantial. For example, uropathogenic, enterohemorrhagic, and extraintestinal types of *E. coli* all display mosaic genome structure, with hundreds of distinct gene islands associated with each type, comprising as much as 40% of the overall gene content in each of these strains.[40] Each pathotype is as distinct from the others as each is from a nonpathogenic laboratory strain of *E. coli*. Conversely, no more than half of the combined gene set is common to all *E. coli* strains. From this and other similar findings arises the concept of the "pan-genome," or the complete set of genes for a species. *E. coli* has a relatively "open" pan-genome in that, with every new genome sequence, a new set of approximately 300 unique genes is discovered, suggesting ongoing evolution of this species by gene acquisition.[41] In contrast, many other pathogens, for instance, *Bacillus anthracis,* have a relatively closed pan-genome.

The sharing of genes among seemingly disparate microorganisms occupying the same niche should in principle provide these microbes with an endless number of combinations of genes for evolutionary experimentation, as it were, within a habitat such as the human intestinal tract.[42] However, a consistent finding from genomic analyses is that most natural populations of microorganisms, including pathogens, consist of only a small number of discrete clonal lineages.[43] This clonal population structure could suggest that the recombination rates of chromosomal genes between different strains of the same species and between different bacterial species are low; that is, only a few evolutionary experiments are attempted. Alternatively, it could imply that, although experimentation may occur aplenty, only a few experiments are "successful" so that emergence of a pathogen is relatively rare. In support of low recombination rates is the finding that even bacteria that possess naturally occurring genetic exchange mechanisms retain their individuality. The pneumococci are a good example of this apparent paradox; despite being naturally transformable and residing in the nasopharynx rich with other bacteria, they have retained a very distinct identity. Thus, despite the unmistakable gene shuffling within and between bacteria, we fail to see homogenization of bacterial species. Rather, bacteria have remained discrete and distinct taxonomic entities[44] because the bacterial chromosome has, in general, resisted rearrangement.

Finally, it is intriguing that most cases of serious disease are caused by only a few of the extant clones that constitute a pathogenic bacterial species. This is exemplified by meningococcal disease, where there is a clear predominance of a particular clone in large areas worldwide with only sporadic disease from other clones. In the case of the typhoid bacillus, there is only one major clone worldwide, although recent antibiotic resistance may be forcing diversity.[45] This is also true for *S. sonnei* and *B. pertussis*, both of which are found as one or a small group of closely related clonal types. Study of *E. coli* populations in the human intestinal tract indicates that only a small number of clonal lineages persist, whereas numerous unrelated cell lines appear and disappear.[43] *E. coli* urinary tract pathogens that cause symptomatic disease in humans may be even less genetically diverse than *E. coli* strains found in the intestinal microbiota or those that cause asymptomatic urinary tract colonization.[46] Perhaps the evolution of these *E. coli* strains to live in a more specialized epithelial niche results in constraints on recombination that preserve their added degree of specialization. This fitness for urinary tract colonization may well be a by-product for improved colonization of its "natural" intestinal niche. Indeed, in some individuals with recurrent urinary tract infections, there can be a simultaneous and identical shift in the dominant *E. coli* population of the bladder and distal gut between one episode and the next.[47] Yet, not all pathogenic bacterial species reveal this pattern of clonal organization. Two notable exceptions are *N. gonorrhoeae* and *Helicobacter pylori*, which appear to use chromosomal recombination quite extensively to increase their genetic diversity. In fact, because of strict human adaptation and extensive genomic diversity and drift, comparative analyses of *H. pylori* genome sequences have revealed important aspects of human migration and human population structure.[48]

REGULATION OF BACTERIAL PATHOGENICITY

If an organism possesses specialized gene products for its virulence, it must be able to use them when needed but not squander its metabolic energy producing them aimlessly. Moreover, indiscriminate expression when not required risks having the virulence determinant detected by host defenses and prematurely neutralized. In consequence, virulence factor expression must be tightly controlled, presenting an additional, yet essential complication of a pathogenic microbe's life.[49] Because the host presents an array of conditions strikingly distinct from those of the outside environment, a pathogen must turn on and off a large number of genes to change its behavior and accommodate its new environment. Because studying gene regulation in the laboratory cannot replicate the host environment, these laboratory findings may not truly represent microbial adaptation to the host; in some cases microbial gene expression can be studied using animal models or using snapshots of infection in humans.

Vibrio cholerae is an excellent example of the agility of gene expression in pathogens. *V. cholerae* is thought to persist in a "viable but nonculturable state" in brackish estuaries and other saline aquatic environments, often associated with the chitinous exoskeleton of various marine organisms.[50] Transition from this milieu to the contrasting environment of the human small intestinal lumen is accompanied by substantial genetic regulatory events, including increased expression of cholera toxin. Further "downstream," the massive increase in the number of vibrios in cholera stools may presage a hyperinfectious state and enhanced transmissibility.[51] The transcriptional profile of these organisms as they exit cholera patients is again different; it reflects the recent nutrient deprivation the pathogen has experienced in the colon and the down-modulation of toxin and chemotactic activity that are no longer needed.[51,52]

Despite its beguiling simplicity, the microbial cell possesses myriad means to rapidly detect, often simultaneously, changes in temperature, ionic conditions, oxygen concentration, pH, and metals such as calcium and iron. These signals often play a dual role; they signal the pathogen that it is in an environment that requires expression of certain virulence determinants, and they are essential for the precise mobilization of virulence determinants. For the gastric commensal pathogen *H. pylori*, and for intestinal pathogens that must traverse the stomach, pH may be a critical signal. The *H. pylori* response to low pH involves changes in transcript abundance for 7% of its genes and is associated with increased motility, perhaps as a means for penetrating the gastric mucous layer.[53] The response of certain pathogens to low iron conditions provides a fine example of how pathogens can turn adversity to their advantage. Iron is a critical component of many cell metabolic processes; therefore it is not surprising that animals have evolved to have high-affinity iron-binding and storage proteins that deprive microorganisms of access to this nutrient, especially at the mucosal surface. However, this strategy can backfire badly on the host. The production of many microbial toxins (e.g., diphtheria toxin) is induced under low iron conditions! Temperature is another obvious signal for microbes adapted to warm-blooded animals that may "come in from the cold." In fact, reversible regulation of the expression of virulence genes by temperature is a feature common to many pathogens, including enteropathogenic and uropathogenic *E. coli* (fimbriae and K-1 capsular antigen), *Shigella* spp. (invasiveness and Shiga toxin), and *Yersinia* spp. (virulence-associated determinants, including outer membrane proteins) (Table 1.4). Thermal regulation of these diverse virulence determinants is mediated by myriad mechanisms: changes in DNA topology, messenger RNA conformation, and protein conformation and stability.[54]

Another common mechanism for recognizing environmental signals and parlaying them into changes in gene expression involves the use of two-component regulatory systems that act on gene expression, usually at the transcriptional level.[55,56] Such systems make use of similar pairs of proteins; one protein of the pair spans the cytoplasmic membrane, contains a transmitter domain, and may act as a sensor of environmental stimuli, whereas the other is a cytoplasmic protein (response regulator) with a receiver domain that regulates responsive genes or proteins. Sensor proteins are often kinases that phosphorylate themselves at a conserved histidine residue. These high-energy intermediates then

TABLE 1.4 Examples of Bacterial Virulence Regulatory Systems

ORGANISM	REGULATORY GENE(S)	ENVIRONMENTAL STIMULI	REGULATED FUNCTIONS
Escherichia coli	*drdX* *fur*	Temperature Iron concentration	Pyelonephritis-associated pili Shiga-like toxin, siderophores
Bordetella pertussis	*bvgAS*	Temperature, ionic conditions, nicotinic acid	Pertussis toxin, filamentous hemagglutinin, adenylate cyclase, others
Vibrio cholerae	*toxR*	Temperature, osmolarity, pH, amino acids	Cholera toxin, pili, outer membrane proteins
Yersinia spp.	*lcr* loci *virF*	Temperature, calcium Temperature	Secretion of effector proteins Adherence, invasiveness
Shigella spp.	*virR*	Temperature	Invasiveness
Salmonella typhimurium	*pag*	pH	Virulence, macrophage survival
Staphylococcus aureus	*agr*	Cell density	α-, β-Hemolysins; toxic shock syndrome toxin 1, protein A

Data from Miller JF, Mekalanos JJ, Falkow S. Coordinate regulation and sensory transduction in the control of bacterial virulence. Science. *1989;243:916–922; and Mekalanos JJ. Environmental signals controlling the expression of virulence determinants in bacteria.* J Bacteriol. *1992;174:1–7.*

transfer their phosphate groups to a conserved aspartate residue within the receiver domain of the response regulator proteins. Competing dephosphorylases determine an overall phosphorylation state of these response regulators, hence their level of activity. Many of these regulators are DNA-binding proteins that regulate transcription of multiple gene targets. Systems of this type control, for example, the permeability properties of the *E. coli* cell envelope in response to osmotic stimuli (EnvZ/OmpR), toxin expression by enterotoxigenic strains of *Bacteroides fragilis* in the presence of colonic mucus (RprX/RprY), expression of numerous virulence factors in *Streptococcus pyogenes* (CovR/CovS), the switch from vegetative growth to sporulation by *Bacillus subtilis* (KinA/SpoOF, SpoOA), and even the ability of the soil bacterium *Agrobacterium tumefaciens* to induce tumors in susceptible plant cells in response to phenols found within plant wound exudates (VirA/VirG).

Pathogenic bacteria can also use small regulatory RNAs (sRNAs) to adapt to environmental stress. As an example, under conditions of low iron, oxidative stress, and membrane stress in the laboratory, *M. tuberculosis* produces an sRNA that inhibits expression of nonessential iron-containing proteins by binding to and compromising cognate mRNAs.[57] Under laboratory conditions, preexposure of *M. tuberculosis* to oxidative stress, followed by iron deprivation, hastens the iron-sparing response, suggesting that sRNAs allow pathogens to integrate multiple environmental signals and anticipate near-term challenges.

Pathogens have the ability to take their own census during infection. This phenomenon called "quorum sensing" is mediated through gene regulation, and it too is not unique to pathogenic bacteria; environmental bacteria keep track of their cell density and regulate their gene expression accordingly.[58] In pathogenic bacteria quorum sensing enables precise choreography of virulence factor production during the course of growth in a vigilant host. For example, in the early stages of a developing soft tissue abscess, *S. aureus* turns on antiphagocytic toxins just as the bacteria reach numbers sufficient to draw the attention of neutrophils.[59] *S. aureus* and other gram-positive bacteria use small peptides to sense cell density and regulate virulence gene expression. For many gram-negative bacteria, quorum sensing and cell-cell communication is achieved by secreting and responding to acylated homoserine lactones. *P. aeruginosa,* the agent of multiple diseases in compromised hosts (as discussed earlier) is activated to produce tissue-degrading enzymes by these autoinducing compounds when they reach sufficient concentration.[60] Quorum sensing is also inextricably linked to the formation of complex bacterial community structures on environmental surfaces; these "biofilms," which can form within the host on both endogenous tissues, such as heart valves, and implanted devices, may enable long-term persistence and resistance to host defenses and antibiotics. *V. cholerae* relies on quorum sensing not only to regulate biofilm formation on marine plankton but also to mediate release from these biofilms upon entry into a human host.[61] The use of quorum sensing for virulence may present therapeutic opportunities: quorum factors may serve as targets for novel therapeutic approaches.[58,62]

These major personality changes in the microbe as it shifts habitat from environmental denizen to host-associated pathogen require a significant "make-over," and it all must be tightly coordinated. The coordinated control of pathogenicity incorporates the important concept of a *regulon.* A regulon is a group of operons or individual genes controlled by a common regulator, usually a protein activator or repressor. This regulator may, in some cases, be the second component of a two-component system. A regulon provides a means by which many genes can respond in concert to a particular stimulus. At other times the same genes may respond independently to other signals. Global regulatory networks are a common feature of microbial virulence and basic microbial physiology (see Table 1.4). In many cases regulatory systems are essential for bacterial virulence. The complexity of virulence regulation in a single microbial pathogen is magnified by the coexistence of multiple interacting (cross-talking) systems and by regulons within regulons. *P. aeruginosa*, an organism with diverse environmental niches, contains genes for 55 sensors and 89 response regulators. In contrast, *H. pylori* contains genes for only 4 and 7, respectively, likely reflecting the more restricted environments it occupies.

Finally, pathogens use complex means of gene regulation not just to cope with host defenses but to evade them altogether. Some pathogens (e.g., various *Neisseria* spp. and *Borrelia* spp.) periodically vary prominent antigenic components of their surface and, by so doing, reduce the chance that the host will mount an adaptive immune response to them. Pili are essential for virulence of gonococci in the human host, probably as a result of their role in adherence to the mucosal target surface.[63,64] But pili, like many bacterial virulence determinants, also elicit specific local and systemic host antibody responses. Intermittent production of pili, as well as variation in pilus composition, are strategies used by gonococci to evade the host immune response. The molecular mechanisms behind these strategies are complex. In general terms phase and antigenic variation result from DNA rearrangements (gene conversion) that move pilin-related transcriptionally silent sequences scattered around the gonococcal chromosome to the expression site (*pilE* locus). Numerous different pilus types may be expressed by derivatives of a single *N. gonorrhoeae* strain.

Gene regulation also underlies the ability of *Borrelia* spp. to establish persistent infections in their mammalian hosts, despite humoral responses directed against antigenic proteins on their surface. Persistence by these pathogens depends upon their mechanisms for varying the expression of host-targeted surface proteins, so as to evade specific neutralizing antibodies. These *Borrelia* mechanisms were first elucidated for the relapsing fever agents, *Borrelia recurrentis* and *Borrelia hermsii*[65,66] but have more recently been characterized for the Lyme disease agent, *Borrelia burgdorferi*.[67] Recombination involving a gene conversion mechanism at the expression site of a surface-associated lipoprotein, VlsE, found on a linear plasmid in the pathogen, allows alternative gene copies from an adjacent tandem silent gene array to become expressed and their antigenically variable proteins to be substituted onto the spirochete surface. VlsE antigenic switching has been shown necessary for persistence of *B. burgdorferi* in mouse models of infection. Although

not yet fully understood at a mechanistic level, this phenomenon may serve as an important new target for adjunctive therapies in the quest to develop and deploy a Lyme disease vaccine. Among other microbial pathogens, DNA rearrangements account for flagellar protein variation in *Salmonella* spp.[68]

CLOSE ENCOUNTERS: PATHOGENS AS CELL BIOLOGISTS

Many bacterial pathogens depend on intimate interactions with host cells to execute their pathogenesis program. These interactions are accomplished because of their ability to hijack host cellular processes, often altering host cell membranes, to achieve any one of several distinct outcomes with respect to the host cell: attachment, phagocytosis, or the avoidance thereof. Attachment or close association with host cells is generally accomplished by pili or other adhesins through direct adherence or through binding to extracellular components. The enteropathogenic and enterohemorrhagic *E. coli,* EPEC and EHEC, respectively, usurp the cell's own machinery to do so. They use a specialized secretion system to form a structure containing reorganized actin that protrudes from the host epithelial cell surface, called a "pedestal" or pseudopod (Fig. 1.1). This pedestal facilitates intimate attachment of the bacterium to the host cell, mediated by the binding of the bacterial adhesin, intimin, to a receptor called Tir. Amazingly, Tir is also a bacterial product. The specialized secretion systems of these bacteria include the determinants required to assemble a supramolecular structure that spans the entire bacterial cell wall and resembles a hypodermic needle[69] that is used to secrete effector molecules directly across host cell membranes. Tir is secreted into the host cell through this "needle" together with other proteins that direct host cell phosphorylation of Tir by activating appropriate host signaling pathways. Tir becomes localized on the host cell membrane at the apical surface of the pedestal.[70] That such a complex series of events was evolutionarily selected to orchestrate this attachment structure is mind-boggling.

Because professional phagocytes—macrophages and neutrophils—are innate immune cells that are ready at hand to be rapidly recruited so as to engulf and kill bacteria, the virulence programs of most pathogens feature mechanisms to avoid phagocytosis by these cells. Capsules of gram-positive bacteria can inhibit their phagocytosis through a variety of mechanisms. Many gram-negative bacteria (e.g., *Yersinia*, *Pseudomonas*, *Vibrio*) use their specialized secretion systems to inject proteins into the host cell. These proteins disrupt the formation of polymeric actin complexes that are required for the forces and changes in membrane conformation that allow for phagocytosis.[71]

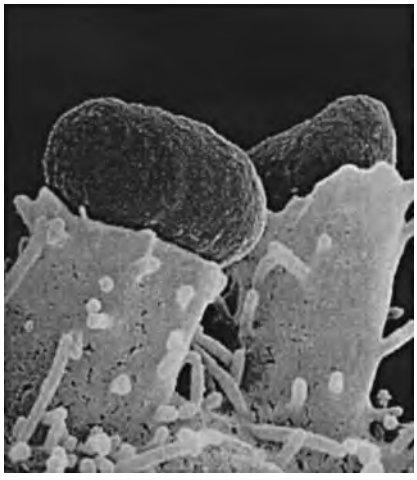

FIG. 1.1 Scanning electron micrograph depicting pseudopod, or "pedestal," formation by enteropathogenic *escherichia coli* (EPEC) as it interacts with the surface of an epithelial cell. This form of intimate adherence requires a bacterial adhesin, intimin; a receptor of bacterial origin, Tir, that is injected into the host cell; and a series of EPEC-initiated signaling events. Disruption of normal absorptive function results in diarrhea. Other bacterial pathogens are also capable of inducing pedestal formation on intestinal epithelial cells. *(From Rosenshine I, Ruschkowski S, Stein M, et al. A pathogenic bacterium triggers epithelial signals to form a functional bacterial receptor that mediates actin pseudopod formation.* EMBO J. *1996;15:2613–2624. Courtesy B.B. Finlay.)*

At the same time, many bacterial pathogens thrive on an intracellular lifestyle for all or a significant portion of their life within the host. Intracellular pathogens must contend with multiple host defenses—reactive oxygen and nitrogen species, antimicrobial peptides, and acidification and hydrolytic enzymes of lysosomes and autophagosomes. In fact, intracellular residence may offer advantages. Pathogens can evade certain host defenses, such as complement and antibodies, and they can find access to otherwise restricted nutrients. Professional phagocytes are formidable would-be adversaries, as killing pathogens is one of their major functions. Yet many bacterial pathogens have evolved the means to enter, survive, multiply, and even persist within the very phagocytes designed to kill bacteria. Residence in phagocytes offers the additional advantage that these cells can transport pathogens across epithelial barriers.

Intracellular pathogens are found in all of the classes listed in Table 1.1. They can be obligate (e.g., *M. tuberculosis, S.* Typhi, *Chlamydia trachomatis*), zoonotic (e.g., *Brucella abortus*, *Rickettsia* spp.), or environmental (e.g., *Mycobacterium marinum* and *Legionella pneumophila*). Of note, commensal pathogens (see Table 1.1) appear to be missing from the known set of intracellular pathogens of humans, suggesting that avoidance of phagocytosis is a stringent requirement for a commensal to establish a niche.

How did pathogens become intracellular dwellers? The relationship of bacteria with eukaryotes is ancient; eukaryotic mitochondria are thought to be derived from a bacterial endosymbiont related to extant rickettsial species. Thus intracellular bacteria may have shaped the very essence of contemporary eukaryotes by giving them the capacity for aerobic respiration. But what about contemporary bacterial pathogens that parasitize professional phagocytes (most commonly, macrophages)? They may have been "trained" to live in macrophages through their ancient encounters with environmental amebae. For many pathogenic mycobacteria, their ability to survive in macrophages tracks completely with their ability to survive in amebae; moreover, pathogenic mycobacteria can grow in macrophages, whereas environmental, nonpathogenic species such as *M. smegmatis* cannot.[72–74] Further support for the idea that amebae provided the evolutionary training ground for intracellular growth in macrophages comes from the finding that mycobacterial virulence factors that promote their growth in macrophages also promote growth in amebae. Similarly, another intracellular human pathogen, *L. pneumophila*, an accidental human pathogen that can cause serious pneumonia, replicates in environmental amebae in the potable water sources responsible for human infection.

Once they are attached to host cells, pathogens use different tricks to enter these cells. Some gain entry through cellular receptors that are normally present, thus subverting their normal function. A pathogen can use multiple receptors to gain entry. For instance, *Chlamydia* can enter via the mannose receptor, the mannose-6-phosphate receptor, and the estrogen receptor, highlighting the stringent need for this obligate intracellular pathogen to become intracellular.[75] Pathogens can also modulate host signaling pathways to gain entry, by binding, for instance, cell surface integrins (e.g., *Yersinia* spp.) and tight-junction–apparatus cadherins (e.g., *Listeria monocytogenes).*[71] For macrophage entry, a pathogen needs a specific ligand to be phagocytosed; a coat of complement or antibody will get it internalized via complement or Fc receptors, respectively. However, many macrophage-adapted pathogens also possess "designer" entry mechanisms. Some pathogens, for instance, *Salmonella* and *Shigella*, can induce cytoskeletal rearrangements on the host cell surface that can then lead to their internalization through macropinocytosis, an endocytic pathway used by cells to internalize extracellular fluid via large endocytic vesicles. In these cases the cytoskeletal rearrangements are induced by specific bacterial proteins that are secreted into host cells upon surface contact. Thus, in general, contact of the pathogen with the host cell surface triggers a signaling cascade in both, indicative of a highly evolved process of coadaptation.[17,18] In accordance, some intracellular pathogens possess multiple proteins that contribute

to a coordinated sequence of cytoskeletal remodeling in the host cell so as to achieve their optimal intracellular niche.

Upon engulfment, bacteria, like other phagocytosed material, find themselves in a plasma membrane-bound compartment. When a nonpathogenic bacterium is internalized by a phagocyte, this compartment, or phagosome, interacts with the cell's endocytic machinery and is ultimately delivered to the lysosome for destruction. Therefore successful intracellular pathogens must have ways around this. Broadly speaking, intracellular pathogens resist destruction by one of two methods: They escape out of the vacuole to gain access to the cytosol as their habitat or they remain inside a vacuole while evading or tolerating the consequences. Access to the cytosol has the advantages of not only avoiding lysosomal degradation but also enabling efficient cell-to-cell spread, and it is a tactic used by diverse pathogens, such as *Listeria*, *Shigella*, and *Rickettsia* spp. *Listeria* uses specific proteins to break out of the initial phagocytic vacuole and then spread to adjoining cells by penetrating the double membrane formed by their apposition. Once in the cytoplasm, *Listeria* replicates and induces its own movement through a remarkable process of host cell actin polymerization and formation of microfilaments within a comet-like tail. *Shigella* also lyses the phagosomal vacuole and induces the formation of similar structures for the purpose of intracytoplasmic movement and cell-cell spread. In both cases bacterial and host factors involved in actin polymerization are distinct, reflecting convergent evolution.[71]

On the other hand, pathogens that remain intravacuolar, for instance, *Salmonella*, *Mycobacterium*, *Legionella,* and *Brucella*, create distinct replication niches in modified endosomal compartments. This is generally accomplished by disrupting normal phagosome maturation so as to live in specialized compartments that are permissive for survival and growth. Many different pathogens have evolved so as to create their own unique phagosome niches by intercepting or exploiting the function of small guanosine triphosphatases (GTPases) called Rabs (Ras-related proteins in brains), which are cellular membrane transport regulators. Some bacteria inhibit phagosome-lysosome fusion to avoid acidified conditions and hydrolytic enzymes or may tolerate compartments fused to lysosomes (*Coxiella burnetii* is an example of the latter). Many pathogens, for instance, mycobacteria, appear to use a two-pronged strategy with specific virulence determinants to both inhibit and tolerate phagosome fusion to lysosomes.[71,76] Finally, intracellular bacteria also have to contend with autophagy, a process through which cellular proteins, lipids, and organelles are targeted to lysosomes for degradation. Bacterial vacuoles can likewise be targeted for autophagic destruction, and most successful intracellular pathogens have diverse strategies to avoid autophagy, or, in some cases, even to exploit it for their growth.[71,77]

Intracellular pathogens can kill host cells from within, either as a means to modulate inflammation or to escape from the cell. A number of pathogens, including *Shigella*, *Salmonella*, *Yersinia,* and *Mycobacterium*, are capable of inducing death of macrophages. Although induction of cell death is a common strategy of many pathogens, each accomplishes this outcome through different mechanisms and with a different precise temporal program.[17] Moreover, the same bacterium can induce different types of cell death, depending on context. For instance, mycobacteria can induce apoptotic cell death through their specialized secretion system, ESX-1, and when tumor necrosis factor levels are dysregulated they can cause programmed necrosis of the macrophage with frank membrane rupture.[25] Each of these processes can affect the development and fate of the tuberculous granuloma. Initially, apoptotic death of an infected macrophage can contribute to new macrophage recruitment and thereby increase cellularity of the granuloma. Phagocytosis of the apoptotic macrophages by new macrophages can provide the mycobacteria with new cellular niches, thus serving to expand intracellular bacterial numbers.[25] Hence the granuloma, for 100 years assigned a central role in "walling off" *M. tuberculosis* infection, can also be a structure built by mycobacteria to promote their expansion and dissemination during early infection. Then with the advent of necrotic macrophage death, bacteria are released to the extracellular environment where they can grow further. Furthermore, necrotic granulomas lead to conditions for increased transmission of infection to new hosts.

IDENTIFICATION AND CHARACTERIZATION OF VIRULENCE GENES

The quest for the molecular basis of bacterial pathogenicity dates back more than 150 years to a time when medical microbiologists were trying to understand the basis of the then rampant toxin-mediated diseases diphtheria and tetanus. Characterization of microbial pathogenicity at the molecular level has traditionally begun with the identification of a virulence-associated phenotype. Such identification may come from clinical observation, epidemiologic investigation, or the use of a model system that reliably reproduces the microbial phenotype. The investigator then tries to identify microbial mutants that no longer have the phenotype. One way to do this is by targeting candidate genes (i.e., genes suspected on the basis of prior information) and then mutating them, often by substituting a mutant gene copy for the wild-type copy using homologous recombination. Nowadays, genome sequences can provide a powerful basis for identifying candidate virulence genes. An alternative agnostic approach is to create a "library" of bacterial mutants, often by using insertional genetic elements (e.g., transposons) as mutational agents and testing these mutants for the loss of the phenotype. Recent variations of this method include creating the library with individually tagged mutants so that after the pooled library is tested in a relevant model of pathogenesis, relevant mutants that failed to produce the phenotype can be more easily identified, a process called negative selection.[78,79] Genetic manipulation of microbes that have so far been genetically intractable (i.e., not amenable to homologous recombination or transposon mutagenesis), such as most fungi and many anaerobes, is increasingly feasible using CRISPR-Cas (clustered regularly interspaced short palindromic repeats–CRISPR associated) protein genome editing tools.[80]

A complementary approach to virulence gene identification comes from asking which bacterial genes are differentially expressed in a relevant pathogenesis model, compared with expression levels in the absence of host cells. These genes are prime candidates for virulence determinants and can then be mutated individually as above. *In vivo expression technology*[81] and *differential fluorescence induction*[82] are approaches based on this concept. Quantitative measurements of coding (gene) and noncoding transcripts, and comparisons of RNA abundance, are greatly facilitated by high-throughput random sequencing of complementary DNA with the generation of millions of expressed sequence tags that are then mapped back to genes and genomes with a method called RNAseq.[83] With RNAseq, gene-specific transcript counts are generated and then used as surrogate measurements for relative gene expression levels.

Through these approaches, genes, RNAs, and their products are incriminated by their relationship with a disease-associated process. Just as the original Henle-Koch postulates have provided a reference point for later revised criteria of microbial causality,[84] a molecular form of Koch's postulates[85] provides a guideline for an experimental approach to the molecular genetic basis of pathogenicity. These postulates continue to coevolve in conjunction with emerging insights into microbial virulence and rapidly improving experimental approaches and technologies. For example, alternative approaches for proof of causation are necessary for pathogens that cannot be isolated and for disease in which a "pathogenic community" is believed to be the cause.[1,86]

Identification of a virulence factor then moves the quest to a new level—to understand how it works. Comparisons of wild-type to mutant bacteria and studies of purified virulence factors, using combinations of biochemical, cell biologic, and immunologic techniques, have both provided insights, as have methods that integrate host responses. As discussed earlier, bacterial virulence factors typically act to counter specific host determinants. For instance, the *Salmonella SipB* gene (secreted by a specialized bacterial secretion system) induces host cell death through its interactions with a host protease called caspase-1. In accordance, in caspase-deficient mice, even wild-type bacteria are attenuated, behaving like the bacterial *SipB* mutant.[87] In a similar vein, methods for monitoring genome-wide host responses have helped to reveal virulence mechanisms.[88,89]

MOLECULAR MICROBIOLOGY AT THE BEDSIDE: PATHOGEN DETECTION, PATHOGEN DISCOVERY, AND GENOMIC PROFILING

As mechanisms of microbial pathogenicity are being revealed, pathogen detection, strain identification, drug resistance, and strain relatedness, as well as patient risk stratification and outcome prediction have all assumed increasing importance in the practice of clinical infectious diseases.[20] For instance, outbreak investigations and infection control both hinge on a precise identification of the etiologic agent. Genome sequences have been immensely beneficial in this regard; they provide a basis for sensitive and specific detection of pathogens and a means for establishing relationships among multiple isolates of the same species. Whole-genome sequencing sometimes provides the only clue that a group of cases are related, that is, that an outbreak of disease has occurred, as well as the relationships of the outbreak strain to other strains. As a result, seemingly unrelated cases occurring during an outbreak have been connected; similarly, geographically or temporally distinct outbreaks have been linked to the same pathogenic clone.[90] Molecular techniques have been used in other epidemiologic investigations to study transmission mechanisms and the role of avirulent microbial variants in the spread of disease. In contrast, traditional approaches, based on phenotypic and general metabolic features of isolates, often fail to indicate the true identity, relationships, and genetic diversity of and among strains.

Molecular, typically sequence-based methods have also revolutionized the search for previously uncharacterized microbial pathogens. There continue to be a vast and frustrating number of poorly explained cases of debilitating illness, including relatively common chronic inflammatory and "autoimmune" syndromes, such as inflammatory bowel disease, sarcoidosis, and various forms of arthritis, that share features with known infectious diseases but for which a microbial agent(s) (see prior discussion of "community as pathogen" earlier) has not been identified.[30,91,92] The principle behind these methods is reliance on molecular signatures to identify or classify a previously unrecognized pathogen; the most commonly used signature is genomic sequence, but other small molecules may prove useful. Phylogenetically reliable sequences, such as highly conserved regions of ribosomal RNA genes, are crucial to the characterization of agents whose sequences do not match exactly those of the agents currently known. These or any sequence can be recovered directly from affected (infected) tissues by amplifying or "capturing" them (by hybridization) from extracted nucleic acids or by random shotgun methods.[91] A critical next step is to assess whether or not the inferred agent has a role in causing the disease in question.[86] A number of organisms resistant to cultivation or propagation have been identified with non–culture-based methods, and cases are made for a role in disease causation.[93–95] It is possible, however, that many of the more easily detected bacterial agents have already been found. The large burden of still unexplained disease with features suggesting infection may be due to agents that have come and gone, agents that currently reside in sequestered anatomic sites in a relatively inactive state, or nonmicrobial causes.

Conceptual advances in our understanding of microbial virulence, revolutionary developments in our technical means, and emerging challenges from a rapidly changing environment around us suggest a number of future scenarios and goals. First, we should focus our efforts on the identification and characterization of pathogens directly from clinical specimens and infected hosts, using cultivation-independent approaches. Manipulation and genome-wide characterization of single bacterial cells is now entirely feasible.[96] Deep sequencing–based pathogen identification from clinical specimens is also a reality.[95,97] We should expect to be able to measure genome-wide microbial transcript abundance and metabolic activity directly from human specimens as well. Second, the composition and function of the indigenous microbial communities can be assessed using metagenomic and other community-wide postgenomic technologies.[98] By combining assessments of community and human response, we stand to gain new insights into the nature of chronic inflammatory disorders of skin and mucosa.[99] Third, we need to fully embrace the importance of host genetic variation in differential susceptibility to infection and subsequent disease.[100] Fourth, genomic and postgenomic technologies enable us to measure and interpret patterns of human gene and protein expression associated with the response to infectious disease; these patterns may serve as the basis for signatures, enabling early recognition and classification of patients on the basis of agent or future disease course.[30,101,102,103] As virulence factors for essential steps in pathogenesis are identified, it should be possible to interfere with their function. As they become better characterized, manipulation of global virulence regulatory systems may be used therapeutically to inhibit entire virulence programs. The result of these efforts should be a more informed and effective approach to the detection, treatment, and prevention of infectious diseases.

DEDICATION

Stanley Falkow, who passed away in May 2018, taught and inspired the other two authors, and many other scientists and clinicians, to appreciate and understand the life strategies of host-associated bacteria. His legendary contributions include the discoveries of the transmissible nature of antibiotic resistance, diverse mechanisms of bacterial pathogenesis, and the creation of a modern molecular version of Koch's postulates as a framework to understand microbial pathogenesis. The authors dedicate this chapter—whose underpinnings and content, like the field of bacterial pathogenesis, owe so much to Stanley—to his memory.

Key References

The complete reference list is available online at Expert Consult.

1. Ley RE, Peterson DA, Gordon JI. Ecological and evolutionary forces shaping microbial diversity in the human intestine. *Cell*. 2006;124:837–848.
2. Dethlefsen L, McFall-Ngai M, Relman DA. An ecological and evolutionary perspective on human-microbe mutualism and disease. *Nature*. 2007;449:811–818.
7. Behr MA, Edelstein PH, Ramakrishnan L. Revisiting the timetable of tuberculosis. *BMJ*. 2018;362:k2738.
11. Lepp PW, Brinig MM, Ouverney CC, et al. Methanogenic Archaea and human periodontal disease. *Proc Natl Acad Sci USA*. 2004;101:6176–6181.
14. Davis KM, Isberg RR. One for all, but not all for one: social behavior during bacterial diseases. *Trends Microbiol*. 2019;27:64–74.
15. Diard M, Garcia V, Maier L, et al. Stabilization of cooperative virulence by the expression of an avirulent phenotype. *Nature*. 2013;494:353–356.
16. Pizarro-Cerda J, Cossart P. Bacterial adhesion and entry into host cells. *Cell*. 2006;124:715–727.
17. Baxt LA, Garza-Mayers AC, Goldberg MB. Bacterial subversion of host innate immune pathways. *Science*. 2013;340:697–701.
18. Merrell DS, Falkow S. Frontal and stealth attack strategies in microbial pathogenesis. *Nature*. 2004;430:250–256.
19. Falkow S. The microbe's view of infection. *Ann Intern Med*. 1998;129:247–248.
20. Relman DA. Microbial genomics and infectious diseases. *N Engl J Med*. 2012;365:347–357.
24. Weddle E, Agaisse H. Principles of intracellular bacterial pathogen spread from cell to cell. *PLoS Pathog*. 2018;14:e1007380.
25. Cambier CJ, Falkow S, Ramakrishnan L. Host evasion and exploitation schemes of *Mycobacterium tuberculosis*. *Cell*. 2014;159:1497–1509.
32. Groisman EA, Ochman H. Pathogenicity islands: bacterial evolution in quantum leaps. *Cell*. 1996;87:791–794.
34. The HC, Thanh DP, Holt KE, et al. The genomic signatures of *Shigella* evolution, adaptation and geographical spread. *Nat Rev Microbiol*. 2016;14:235–250.
35. Rascovan N, Sjögren KG, Kristiansen K, et al. Emergence and spread of basal lineages of *Yersinia pestis* during the Neolithic decline. *Cell*. 2019;176:295–305.e10.
36. Moran NA. Microbial minimalism: genome reduction in bacterial pathogens. *Cell*. 2002;108:583–586.
41. Rasko DA, Rosovitz MJ, Myers GS, et al. The pangenome structure of *Escherichia coli*: comparative genomic analysis of *E. coli* commensal and pathogenic isolates. *J Bacteriol*. 2008;190:6881–6893.
42. Smillie CS, Smith MB, Friedman J, et al. Ecology drives a global network of gene exchange connecting the human microbiome. *Nature*. 2011;480:241–244.
49. Guiney DG. Regulation of bacterial virulence gene expression by the host environment. *J Clin Invest*. 1997;99:565–569.
51. Merrell DS, Butler SM, Qadri F, et al. Host-induced epidemic spread of the cholera bacterium. *Nature*. 2002;417:642–645.
54. Fang FC, Frawley ER, Tapscott T, et al. Bacterial stress responses during host infection. *Cell Host Microbe*. 2016;20:133–143.
58. Whiteley M, Diggle SP, Greenberg EP. Progress in and promise of bacterial quorum sensing research. *Nature*. 2017;551:313–320.
62. Rutherford ST, Bassler BL. Bacterial quorum sensing: its role in virulence and possibilities for its control. *Cold Spring Harb Perspect Med*. 2012;2:a012427.
67. Palmer GH, Bankhead T, Seifert HS. Antigenic variation in bacterial pathogens. *Microbiol Spectr*. 2016;4.
70. Kenny B, DeVinney R, Stein M, et al. Enteropathogenic *E. coli* (EPEC) transfers its receptor for intimate adherence into mammalian cells. *Cell*. 1997;91:511–520.
71. Asrat S, de Jesús DA, Hempstead AD, et al. Bacterial pathogen manipulation of host membrane trafficking. *Annu Rev Cell Dev Biol*. 2014;30:79–109.

77. Huang J, Brumell JH. Bacteria-autophagy interplay: a battle for survival. *Nat Rev Microbiol*. 2014;12:101–114.
80. Strich JR, Chertow DS. CRISPR-Cas biology and infectious diseases applications. *J Clin Microbiol*. 2019;57:e01307-18.
83. Saliba AE, Santos SC, Vogel J. New RNA-seq approaches for the study of bacterial pathogens. *Curr Opin Microbiol*. 2017;35:78–87.
85. Falkow S. Molecular Koch's postulates applied to microbial pathogenicity. *Rev Infect Dis*. 1988;10:S274–S276.
86. Fredricks DN, Relman DA. Sequence-based identification of microbial pathogens: a reconsideration of Koch's postulates. *Clin Microbiol Rev*. 1996;9:18–33.
90. Reuter S, Ellington MJ, Cartwright EJ, et al. Rapid bacterial whole-genome sequencing to enhance diagnostic and public health microbiology. *JAMA Intern Med*. 2013;173:1397–1404.
91. Relman DA. The search for unrecognized pathogens. *Science*. 1999;284:1308–1310.
93. Relman DA, Loutit JS, Schmidt TM, et al. The agent of bacillary angiomatosis. An approach to the identification of uncultured pathogens. *N Engl J Med*. 1990;323:1573–1580.
94. Chang Y, Cesarman E, Pessin MS, et al. Identification of herpesvirus-like DNA sequences in AIDS-associated Kaposi's sarcoma. *Science*. 1994;266:1865–1869.
97. Loman NJ, Constantinidou C, Christner M, et al. A culture-independent sequence-based metagenomics approach to the investigation of an outbreak of Shiga-toxigenic *Escherichia coli* O104:H4. *JAMA*. 2013;309:1502–1510.
98. The Human Microbiome Project Consortium. Structure, function and diversity of the healthy human microbiome. *Nature*. 2012;486:207–214.
100. Casanova JL, Abel L. Human genetics of infectious diseases: unique insights into immunological redundancy. *Semin Immunol*. 2018;36:1–12.
102. Sweeney TE, Wong HR, Khatri P. Robust classification of bacterial and viral infections via integrated host gene expression diagnostics. *Sci Transl Med*. 2016;8:346ra91.

References

1. Ley RE, Peterson DA, Gordon JI. Ecological and evolutionary forces shaping microbial diversity in the human intestine. *Cell*. 2006;124:837–848.
2. Dethlefsen L, McFall-Ngai M, Relman DA. An ecological and evolutionary perspective on human-microbe mutualism and disease. *Nature*. 2007;449:811–818.
3. Sender R, Fuchs S, Milo R. Are we really vastly outnumbered? Revisiting the ratio of bacterial to host cells in humans. *Cell*. 2016;164:337–340.
4. Chung H, Pamp SJ, Hill JA, et al. Gut immune maturation depends on colonization with a host-specific microbiota. *Cell*. 2012;149:1578–1593.
5. Bohnhoff M, Drake BL, Miller CP. Effect of streptomycin on susceptibility of intestinal tract to experimental *Salmonella* infection. *Proc Soc Exp Biol Med*. 1954;86:132–137.
6. Horz HP, Robertz N, Vianna ME, et al. Relationship between methanogenic archaea and subgingival microbial complexes in human periodontitis. *Anaerobe*. 2015;35(Pt A):10–12.
7. Behr MA, Edelstein PH, Ramakrishnan L. Revisiting the timetable of tuberculosis. *BMJ*. 2018;362:k2738.
8. Avanzi C, Del-Pozo J, Benjak A, et al. Red squirrels in the British Isles are infected with leprosy bacilli. *Science*. 2016;354:744–747.
9. Sharma R, Singh P, Loughry WJ, et al. Zoonotic leprosy in the southeastern United States. *Emerg Infect Dis*. 2015;21:2127–2134.
10. Garrett WS, Lord GM, Punit S, et al. Communicable ulcerative colitis induced by T-bet deficiency in the innate immune system. *Cell*. 2007;131:33–45.
11. Lepp PW, Brinig MM, Ouverney CC, et al. Methanogenic Archaea and human periodontal disease. *Proc Natl Acad Sci USA*. 2004;101:6176–6181.
12. Eckburg PB, Lepp PW, Relman DA. Archaea and their potential role in human disease. *Infect Immun*. 2003;71:591–596.
13. Vianna ME, Holtgraewe S, Seyfarth I, et al. Quantitative analysis of three hydrogenotrophic microbial groups, methanogenic Archaea, sulfate-reducing bacteria, and acetogenic bacteria, within plaque biofilms associated with human periodontal disease. *J Bacteriol*. 2008;190:3779–3785.
14. Davis KM, Isberg RR. One for all, but not all for one: social behavior during bacterial diseases. *Trends Microbiol*. 2019;27:64–74.
15. Diard M, Garcia V, Maier L, et al. Stabilization of cooperative virulence by the expression of an avirulent phenotype. *Nature*. 2013;494:353–356.
16. Pizarro-Cerda J, Cossart P. Bacterial adhesion and entry into host cells. *Cell*. 2006;124:715–727.
17. Baxt LA, Garza-Mayers AC, Goldberg MB. Bacterial subversion of host innate immune pathways. *Science*. 2013;340:697–701.
18. Merrell DS, Falkow S. Frontal and stealth attack strategies in microbial pathogenesis. *Nature*. 2004;430:250–256.
19. Falkow S. The microbe's view of infection. *Ann Intern Med*. 1998;129:247–248.
20. Relman DA. Microbial genomics and infectious diseases. *N Engl J Med*. 2012;365:347–357.
21. Klemm E, Dougan G. Advances in understanding bacterial pathogenesis gained from whole-genome sequencing and phylogenetics. *Cell Host Microbe*. 2016;19:599–610.
22. Relman DA, Falkow S. The meaning and impact of the human genome sequence for microbiology. *Trends Microbiol*. 2001;9:206–208.
23. Kolenbrander PE, Palmer RJ, Periasamy S, et al. Oral multispecies biofilm development and the key role of cell-cell distance. *Nature Rev Microbiol*. 2010;8:471–480.
24. Weddle E, Agaisse H. Principles of intracellular bacterial pathogen spread from cell to cell. *PLoS Pathog*. 2018;14:e1007380.
25. Cambier CJ, Falkow S, Ramakrishnan L. Host evasion and exploitation schemes of *Mycobacterium tuberculosis*. *Cell*. 2014;159:1497–1509.
26. Young D, Hussell T, Dougan G. Chronic bacterial infections: living with unwanted guests. *Nat Immunol*. 2002;3:1026–1032.
27. Jonathan R, Davis JR, Lederberg J, eds. *Emerging Infectious Diseases From the Global to the Local Perspective: A Summary of a Workshop of the Forum on Emerging Infections. Board on Global Health*. Washington, DC: Institute of Medicine, National Academy Press; 2001.
28. Jones KE, Patel NG, Levy MA, et al. Global trends in emerging infectious diseases. *Nature*. 2008;451:990–993.
29. Carroll D, Daszak P, Wolfe ND, et al. The global virome project. *Science*. 2018;359:872–874.
30. Relman DA. New technologies, human-microbe interactions, and the search for previously unrecognized pathogens. *J Infect Dis*. 2002;186(suppl 2):S254–S258.
31. Fleischmann RD, Adams MD, White O, et al. Whole-genome random sequencing and assembly of *Haemophilus influenzae* Rd. *Science*. 1995;269:496–512.
32. Groisman EA, Ochman H. Pathogenicity islands: bacterial evolution in quantum leaps. *Cell*. 1996;87:791–794.
33. Galán JE. Typhoid toxin provides a window into typhoid fever and the biology of *Salmonella* Typhi. *Proc Natl Acad Sci USA*. 2016;113:6338–6344.
34. The HC, Thanh DP, Holt KE, et al. The genomic signatures of *Shigella* evolution, adaptation and geographical spread. *Nat Rev Microbiol*. 2016;14:235–250.
35. Rascovan N, Sjögren KG, Kristiansen K, et al. Emergence and spread of basal lineages of *Yersinia pestis* during the Neolithic decline. *Cell*. 2019;176:295–305.e10.
36. Moran NA. Microbial minimalism: genome reduction in bacterial pathogens. *Cell*. 2002;108:583–586.
37. Parkhill J, Sebaihia M, Preston A, et al. Comparative analysis of the genome sequences of *Bordetella pertussis, Bordetella parapertussis* and *Bordetella bronchiseptica*. *Nat Genet*. 2003;35:32–40.
38. Cummings CA, Brinig MM, Lepp PW, et al. *Bordetella* species are distinguished by patterns of substantial gene loss and host adaptation. *J Bacteriol*. 2004;186:1484–1492.
39. Weigand MR, Peng Y, Loparev V, et al. The history of *Bordetella pertussis* genome evolution includes structural rearrangement. *J Bacteriol*. 2017;199:pii: e00806-16.
40. Welch RA, Burland V, Plunkett G 3rd, et al. Extensive mosaic structure revealed by the complete genome sequence of uropathogenic *Escherichia coli*. *Proc Natl Acad Sci USA*. 2002;99:17020–17024.
41. Rasko DA, Rosovitz MJ, Myers GS, et al. The pangenome structure of *Escherichia coli*: comparative genomic analysis of *E. coli* commensal and pathogenic isolates. *J Bacteriol*. 2008;190:6881–6893.
42. Smillie CS, Smith MB, Friedman J, et al. Ecology drives a global network of gene exchange connecting the human microbiome. *Nature*. 2011;480:241–244.
43. Achtman M. Evolution, population structure, and phylogeography of genetically monomorphic bacterial pathogens. *Annu Rev Microbiol*. 2008;62:53–70.
44. Falkow S. The evolution of pathogenicity in *Escherichia, Shigella,* and *Salmonella*. In: Neidhardt FC, ed. *Escherichia Coli and Salmonella Typhimurium*. Washington, DC: American Society for Microbiology Press; 1996:2723–2729.
45. Roumagnac P, Weill FX, Dolecek C, et al. Evolutionary history of *Salmonella typhi*. *Science*. 2006;314:1301–1304.
46. Johnson JR, Manges AR, O'Bryan TT, et al. A disseminated multidrug-resistant clonal group of uropathogenic *Escherichia coli* in pyelonephritis. *Lancet*. 2002;359:2249–2251.
47. Chen SL, Wu M, Henderson JP, et al. Genomic diversity and fitness of *E. coli* strains recovered from the intestinal and urinary tracts of women with recurrent urinary tract infection. *Sci Transl Med*. 2013;5:184ra60.
48. Moodley Y, Linz B, Yamaoka Y, et al. The peopling of the Pacific from a bacterial perspective. *Science*. 2009;323:527–530.
49. Guiney DG. Regulation of bacterial virulence gene expression by the host environment. *J Clin Invest*. 1997;99:565–569.
50. Lipp EK, Huq A, Colwell RR. Effects of global climate on infectious disease: the cholera model. *Clin Microbiol Rev*. 2002;15:757–770.
51. Merrell DS, Butler SM, Qadri F, et al. Host-induced epidemic spread of the cholera bacterium. *Nature*. 2002;417:642–645.
52. Bina J, Zhu J, Dziejman M, et al. ToxR regulon of *Vibrio cholerae* and its expression in vibrios shed by cholera patients. *Proc Natl Acad Sci USA*. 2003;100:2801–2806.
53. Merrell DS, Goodrich ML, Otto G, et al. pH-regulated gene expression of the gastric pathogen *Helicobacter pylori*. *Infect Immun*. 2003;71:3529–3539.
54. Fang FC, Frawley ER, Tapscott T, et al. Bacterial stress responses during host infection. *Cell Host Microbe*. 2016;20:133–143.
55. Zschiedrich CP, Keidel V, Szurmant H. Molecular mechanisms of two-component signal transduction. *J Mol Biol*. 2016;428:3752–3775.
56. Groisman EA. Feedback control of two-component regulatory systems. *Annu Rev Microbiol*. 2016;70:103–124.
57. Gerrick ER, Barbier T, Chase MR, et al. Small RNA profiling in *Mycobacterium tuberculosis* identifies MrsI as necessary for an anticipatory iron sparing response. *Proc Natl Acad Sci USA*. 2018;115:6464–6469.
58. Whiteley M, Diggle SP, Greenberg EP. Progress in and promise of bacterial quorum sensing research. *Nature*. 2017;551:313–320.
59. Novick RP, Geisinger E. Quorum sensing in staphylococci. *Annu Rev Genet*. 2008;42:541–564.
60. Donlan RM, Costerton JW. Biofilms: survival mechanisms of clinically relevant microorganisms. *Clin Microbiol Rev*. 2002;15:167–193.
61. Zhu J, Mekalanos JJ. Quorum sensing–dependent biofilms enhance colonization in *Vibrio cholerae*. *Dev Cell*. 2003;5:647–656.
62. Rutherford ST, Bassler BL. Bacterial quorum sensing: its role in virulence and possibilities for its control. *Cold Spring Harb Perspect Med*. 2012;2:a012427.
63. Hobbs MM, Sparling PF, Cohen MS, et al. Experimental gonococcal infection in male volunteers: cumulative experience with *Neisseria gonorrhoeae* strains FA1090 and MS11mkC. *Front Microbiol*. 2011;2:123.
64. Anderson MT, Dewenter L, Maier B, et al. Seminal plasma initiates a *Neisseria gonorrhoeae* transmission state. *MBio*. 2014;5:e1004–e1013.
65. Borst P. Antigenic variation and allelic exclusion. *Cell*. 2002;109:5–8.
66. Meier JT, Simon MI, Barbour AG. Antigenic variation is associated with DNA rearrangements in a relapsing fever *Borrelia*. *Cell*. 1985;41:403–409.
67. Palmer GH, Bankhead T, Seifert HS. Antigenic variation in bacterial pathogens. *Microbiol Spectr*. 2016;4.
68. Simon M, Zieg J, Silverman M, et al. Phase variation: evolution of a controlling element. *Science*. 1980;209:1370–1374.
69. Kubori T, Sukhan A, Aizawa SI, et al. Molecular characterization and assembly of the needle complex of the *Salmonella typhimurium* type III protein secretion system. *Proc Natl Acad Sci USA*. 2000;97:10225–10230.
70. Kenny B, DeVinney R, Stein M, et al. Enteropathogenic *E. coli* (EPEC) transfers its receptor for intimate adherence into mammalian cells. *Cell*. 1997;91:511–520.
71. Asrat S, de Jesús DA, Hempstead AD, et al. Bacterial pathogen manipulation of host membrane trafficking. *Annu Rev Cell Dev Biol*. 2014;30:79–109.
72. Laencina L, Dubois V, Le Moigne V, et al. Identification of genes required for *Mycobacterium abscessus* growth in vivo with a prominent role of the ESX-4 locus. *Proc Natl Acad Sci USA*. 2018;115:E1002–E1011.
73. Cirillo JD, Falkow S, Tompkins LS, et al. Interaction of *Mycobacterium avium* with environmental amoebae enhances virulence. *Infect Immun*. 1997;65:3759–3767.
74. Bakala N'Goma JC, Le Moigne V, Soismier N, et al. *Mycobacterium abscessus* phospholipase C expression is induced during coculture within amoebae and enhances *M. abscessus* virulence in mice. *Infect Immun*. 2015;83:780–791.
75. Bastidas RJ, Elwell CA, Engel JN, et al. Chlamydial intracellular survival strategies. *Cold Spring Harb Perspect Med*. 2013;3:a010256.
76. Levitte S, Adams KN, Berg RD, et al. Mycobacterial acid tolerance enables phagolysosomal survival and establishment of tuberculous infection in vivo. *Cell Host Microbe*. 2016;20:250–258.
77. Huang J, Brumell JH. Bacteria-autophagy interplay: a battle for survival. *Nat Rev Microbiol*. 2014;12:101–114.
78. Hensel M, Shea JE, Gleeson C, et al. Simultaneous identification of bacterial virulence genes by negative selection. *Science*. 1995;269:400–403.
79. Cummins J, Gahan CG. Signature tagged mutagenesis in the functional genetic analysis of gastrointestinal pathogens. *Gut Microbes*. 2012;3:93–103.
80. Strich JR, Chertow DS. CRISPR-Cas biology and infectious diseases applications. *J Clin Microbiol*. 2019;57:e01307-18.
81. Angelichio MJ, Camilli A. In vivo expression technology. *Infect Immun*. 2002;70:6518–6523.
82. Valdivia RH, Falkow S. Fluorescence-based isolation of bacterial genes expressed within host cells. *Science*. 1997;277:2007–2011.
83. Saliba AE, Santos SC, Vogel J. New RNA-seq approaches for the study of bacterial pathogens. *Curr Opin Microbiol*. 2017;35:78–87.
84. Evans AS. Causation and disease: the Henle-Koch postulates revisited. *Yale J Biol Med*. 1976;49:175–195.
85. Falkow S. Molecular Koch's postulates applied to microbial pathogenicity. *Rev Infect Dis*. 1988;10:S274–S276.
86. Fredricks DN, Relman DA. Sequence-based identification of microbial pathogens: a reconsideration of Koch's postulates. *Clin Microbiol Rev*. 1996;9:18–33.
87. Monack DM, Hersh D, Ghori N, et al. *Salmonella* exploits caspase-1 to colonize Peyer's patches in a murine typhoid model. *J Exp Med*. 2000;192:249–258.
88. Irazoqui JE, Troemel ER, Feinbaum RL, et al. Distinct pathogenesis and host responses during infection of *C. elegans* by *P. aeruginosa* and *S. aureus*. *PLoS Pathog*. 2010;6:e1000982.
89. Belcher CE, Drenkow J, Kehoe B, et al. The transcriptional responses of respiratory epithelial cells to

Bordetella pertussis reveal host defensive and pathogen counter-defensive strategies. *Proc Natl Acad Sci USA*. 2000;97:13847–13852.
90. Reuter S, Ellington MJ, Cartwright EJ, et al. Rapid bacterial whole-genome sequencing to enhance diagnostic and public health microbiology. *JAMA Intern Med*. 2013;173:1397–1404.
91. Relman DA. The search for unrecognized pathogens. *Science*. 1999;284:1308–1310.
92. Pallen MJ, Loman NJ, Penn CW. High-throughput sequencing and clinical microbiology: progress, opportunities and challenges. *Curr Opin Microbiol*. 2010;13:625–631.
93. Relman DA, Loutit JS, Schmidt TM, et al. The agent of bacillary angiomatosis. An approach to the identification of uncultured pathogens. *N Engl J Med*. 1990;323:1573–1580.
94. Chang Y, Cesarman E, Pessin MS, et al. Identification of herpesvirus-like DNA sequences in AIDS-associated Kaposi's sarcoma. *Science*. 1994;266:1865–1869.
95. Wilson MR, O'Donovan BD, Gelfand JM, et al. Chronic meningitis investigated via metagenomic next-generation sequencing. *JAMA Neurol*. 2018;75:947–955.
96. Lasken RS. Genomic sequencing of uncultured microorganisms from single cells. *Nat Rev Microbiol*. 2012;10:631–640.
97. Loman NJ, Constantinidou C, Christner M, et al. A culture-independent sequence-based metagenomics approach to the investigation of an outbreak of Shiga-toxigenic *Escherichia coli* O104:H4. *JAMA*. 2013;309:1502–1510.
98. The Human Microbiome Project Consortium. Structure, function and diversity of the healthy human microbiome. *Nature*. 2012;486:207–214.
99. Haberman Y, Karns R, Dexheimer PJ, et al. Ulcerative colitis mucosal transcriptomes reveal mitochondriopathy and personalized mechanisms underlying disease severity and treatment response. *Nat Commun*. 2019;10:38.
100. Casanova JL, Abel L. Human genetics of infectious diseases: unique insights into immunological redundancy. *Semin Immunol*. 2018;36:1–12.
101. Boldrick JC, Alizadeh AA, Diehn M, et al. Stereotyped and specific gene expression programs in human innate immune responses to bacteria. *Proc Natl Acad Sci USA*. 2002;99:972–977.
102. Sweeney TE, Wong HR, Khatri P. Robust classification of bacterial and viral infections via integrated host gene expression diagnostics. *Sci Transl Med*. 2016;8:346ra91.
103. Sweeney TE, Perumal TM, Henao R, et al. A community approach to mortality prediction in sepsis via gene expression analysis. *Nat Commun*. 2018;9:694.

2 The Human Microbiome of Local Body Sites and Their Unique Biology

Kjersti Aagaard, Ruth Ann Luna, and James Versalovic

DEFINING THE HUMAN MICROBIOME

The human microbiota can be defined as all microorganisms (approximately 90 trillion bacteria, archaea, eukaryotic microbes, and viruses) residing in the human body; the human microbiome consists of the genes and gene products (RNA, proteins, metabolites) produced by resident microbial communities. The advent of high-throughput DNA and RNA sequencing technologies and computational methodologies has enabled scientists to systematically catalog the global set of microorganisms—cultured and uncultured—in a heretofore unparalleled manner. Different body habitats contain microbial communities and microbiomes that differ by microbial composition and function (metabolic modules and pathways). As a result, each body habitat is composed of characteristic bacterial species and other microbial taxa that are adapted to each body site. Differences in microbial composition yield differences in metabolic capacity and aggregate function of the human microbiome.

Traditional notions have been challenged, such as the ideas first put forth in Koch's postulates, whereby microbes were viewed as pathogens and as sole etiologic agents of infectious diseases. Such a "foe" view neglects our earliest sightings of oral and fecal microbes with Anton van Leeuwenhoek's microscopes, where it was observed that *animalcules* (microorganisms) reside in a symbiotic and likely mutually beneficial relationship with the host. We now appreciate that the microbial genome exceeds the human genome by at least 250-fold, and the cellular count of resident microbiota matches and slightly exceeds the human cell count.[1] Our concepts regarding the relative abundance and ubiquity of diverse human pathogens are growing more profoundly with advances in the science of the human microbiome. *Abundance* refers to the relative quantity of microbes within each individual or body site, whereas *ubiquity* refers to the presence of the same microbes in different individuals.

The Human Microbiome Project (HMP) documented the striking absence of canonical pathogens in healthy adults at 18 body sites.[2] Notable exceptions were the well-known pathogens *Staphylococcus aureus* and *Escherichia coli*. As an example, *E. coli* DNA was detected in 15% of individuals at 0.5% abundance and was detectable at any level in 61% of healthy adults. Canonical pathogens as defined by the National Institute of Allergy and Infectious Diseases[2] are generally absent from the human microbiome in healthy individuals, but opportunistic pathogens are widely distributed in healthy adults. A total of 59 opportunistic pathogens in the Pathosystems Resource Integration Center (PATRIC) database were detected in 242 healthy adults, and these species were shared in colonized individuals across multiple body sites. This finding contrasts with the relative habitat specificity of commensal species that lack evidence of pathogenicity. In summary, although canonical pathogens are rare in healthy individuals, opportunistic pathogens are relatively common in healthy individuals and explain why immunosuppression often results in opportunistic infections. Canonical pathogens, by contrast, must be transmitted to healthy individuals from other humans, animals, or the environment. Opportunistic pathogens may arise from within the indigenous microbiome, in addition to possible transmission from outside sources.

The Human Microbiome as a Complex Ecosystem Composed of Multiple Body Site Habitats and Niches

The HMP (funded by the US National Institutes of Health) and Metagenomics of the Human Intestinal Tract (MetaHIT; funded by the European Commission) initiatives established the first microbial gene catalogs of the human adult microbiota; the HMP effort spanned 15 body site niches in men and 18 in women.[1–4] Each primary body habitat in the healthy human microbiome contains a distinctive microbial community, when evaluated according to bacterial composition[2,3,5,6] (Fig. 2.1). Furthermore, the HMP reported that although no bacterial taxa were universally present among all body habitats and individuals, the relative distribution of several metabolic modules and pathways was surprisingly similar, with a greater degree of similarity observed within ethnic and racial groups.[2] On a population-wide scale, the greatest variation in both composition and function is observed when comparing one body niche to another. The next level of microbiome variation is observed when comparing composition and function between individuals of different health and disease states; geographic distribution; race, ethnicity, or both; and life stage. Relatively low-level variation is observed when comparing same body niches among similar groups of individuals in a relatively homogeneous population. In other words, our microbiomes are most distinct when comparing one body niche to another (i.e., gut to vagina, or oral to skin) and relatively less distinct when comparing among individuals (i.e., gut to gut). Expanded analysis of the original HMP cohort (HMP1 II) summarized strain-level variation from a comprehensive data set derived from 2355 metagenomes and 265 individuals.[99] Bacterial strain profiles were stable over time, with the identification of body site–specific subspecies clades. For example, *Haemophilus parainfluenzae* yields distinct subspecies clades in the oral cavity. The Bacteroidetes species contributed to personalized microbial composition of the intestine, compared with other body sites. Multicore metabolic pathways were identified as relatively human specific and included vitamin B_{12} biosynthesis as an example of a human microbiome–enriched pathway.

As a result, our rapidly evolving view of the human ecosystem augments the traditional view of a single pathogen being responsive for disease onset. Even if a single microbe is the etiologic agent of infection, the pathogenesis and pathophysiology of infection can be viewed within the context of the microbiome and human biology. We now appreciate that our human microbiome is a complex ecosystem, with distinct biologic niches. The resultant perspective for human health and disease shifts the focus to the global balance of our microbiota rather than the appearance of a specific infectious agent. As a result, a clear understanding of the role of microbial community structure in the host can facilitate a deeper understanding of infectious diseases and susceptibility to infections (Table 2.1). We are realizing the translational fruits of a broadened understanding of the human microbiome as metagenomic medicine makes strides in restoring health in highly morbid conditions (e.g., recurrent *Clostridioides difficile* [formerly *Clostridium difficile*] colitis).[7]

This chapter describes the current state of knowledge of the origin of the human microbiome and key features of human-associated microbial

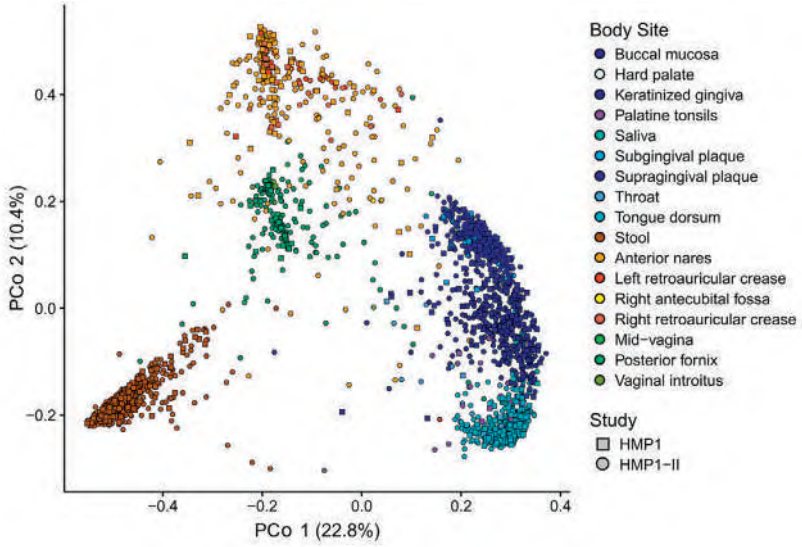

FIG. 2.1 The human microbiome is composed of distinct bacterial populations at different body sites. This principal components *(PCo)* analysis plot shows each distinct body site (indicated by distinct colors) and its microbial composition in healthy adults. Each colored circle in space represents an individual's microbiome as determined by 16S rRNA gene sequencing, and similar microbiomes are grouped more closely together in two-dimensional space. *HMP,* Human Microbiome Project. *(Modified from Lloyd-Price J, Mahurkar A, et al. Strains, functions and dynamics in the expanded Human Microbiome Project.* Nature. *2017;550:61–66.)*

communities in each primary body habitat. We render brief discussions regarding known determinants of the microbial structure of these niches and presumptive associations with several disease states (as examples).

From Whence and When Do Our Microbiomes Come?

It had long been thought that mammalian neonates were first exposed and colonized with microbiota during birth (intrapartum and parturition). However, multiple lines of evidence have converged to suggest that first exposure to microorganisms likely occurs in utero.[8–10,11–14,15–17,18] Although it is not clear whether this earliest microbial exposure results in true live colonization of the fetus or rather enables immune tolerance for later ex utero colonization of the neonate, it is evident that neonates are born with detectable microbes present, and they expand during early infancy to form relatively complex compositional and functional communities with the same body niche separation found in adults[8,14–17,19–36,37–42,43,44]

What are these lines of evidence supporting predelivery microbial exposure? They are numerous and come from not only DNA (i.e., metagenomic) level evidence, but also from cultivation and targeted bacterial species and strain analyses. First, the uterus and its endometrium is clearly not sterile, and an association between endometrial microbes and reproductive success has recently been suggested.[45–49,50,51–57,58,59] Second, the placenta of multiple mammalian species harbors a low-biomass, low-diversity microbiome that can be detected by metagenomics, immunohistochemistry, cultivation, or a combination and is distinguishable from potential "kit" or "DNA extraction buffer" contamination.[40–42,48,60–68,69,70,71–76,77–80,81] Although one group reported an inability to distinguish detection of taxa in the microbiome from "kit negative" and "environmental" controls, their analysis was limited to 16S rRNA gene-based taxa profiles based on V1V2 amplicon sequencing.[82] Moreover, shared taxa at a coarse level (i.e., above species or strain) does not establish contamination. Thus the preponderance of evidence available supports the presence of a low-biomass placental microbial community. Third, as noted previously, the neonate is not born sterile.[8,14–17,19–37,38–44] Fourth, exposures during pregnancy leave a lasting "footprint" on the offspring. Specifically, early factors potentially influencing the neonatal and infant microbiome include gestational age at delivery,[17] infant feeding patterns,[18,83] maternal high-fat diet intake throughout gestation and lactation,[9,19] antibiotic use,[84] and environmental exposures.[85,86] Fifth, there are mixed data concerning whether or not mode of delivery (cesarean versus vaginal) has a lasting impact on the structure and function of the neonatal and infant microbiome. Based on several recent studies, a meta-analysis, and expert committee opinions,[15,33,35,36,87,88–90,91–97,98] we and others support the conclusion that the long-term impact of mode of delivery on the composition and function of the human microbiome is likely minimal, modulated by multiple confounders and collinear factors, and largely limited to neonatal (<28 days after birth) and early infant life. Given the numerous and significant confounding factors in many studies comparing microbiota after cesarean and vaginal birth, it is presently difficult to state that the act of delivering via cesarean in and of itself confers dysbiosis to the offspring, let alone what species or strains might be responsible for disease risk later in life.

What then explains multiple studies suggesting an association between cesarean delivery and several microbiome-related health outcomes? In terms of the longitudinal establishment of the human microbiome, it was initially published and thought that the microbiomes in vaginally delivered versus cesarean-delivered infants yielded a modest difference at up to 6 months of age and appreciable differences years later.[99–101] However, more recent studies indicate that the human microbiome effectively "differentiates" at each body site by 6 to 8 weeks of age, and the effects of delivery mode largely subside by 2 months of age.[8,19] It was initially believed that neonates delivered by cesarean section have a characteristic deficiency of *Bifidobacterium* spp., whereas infants delivered vaginally have a predominance of *Bifidobacterium longum* and *Bifidobacterium catenulatum,* but these observations may be confounded by other factors such as maternal diet and breast-feeding.[33,85,89,99,102–106] In other words, both sets of observations can hold true. Although there may be an association between cesarean birth and several chronic, noncommunicable diseases (asthma, atopic allergies, obesity, type 2 diabetes mellitus), the act of the surgery is unlikely to change the microbiome community. Rather, the company that cesarean delivery keeps (such as underlying medical indication for the cesarean delivery and lower rates of exclusive human milk feeding) may be the primary factors. Thus, efforts aimed at reducing medical indications for cesarean and increasing exclusive human milk feeding may prove to be optimal.[87]

Is the capacity to influence our microbiome limited to early life? Clearly not. These same influential factors continue through adult life, with development and succession of the microbiome occurring during the human lifetime. Population-based studies have identified multiple factors that relate to observed variance in the composition, gene content, and function of the human microbiome. These factors include body habitat,[107,108] age,[109] environmental exposures (chemical and microbiologic), chronic disease,[110,111] genetics,[112] sex,[113] socioeconomic status,[20] geography,[109] and diet.[109,114] Although much has been made of the impact

TABLE 2.1 Explanation of Key Terms

TERM	DEFINITION
Biologic Terms	
Community structure	Used most commonly to refer to the taxonomic composition of a microbial community; can also refer to the spatiotemporal distribution of taxa
Diversity	A measure of the taxonomic distribution within a community, either in terms of distinct taxa or in terms of their evolutionary or phylogenetic distance
Dysbiosis	Abnormal distribution or quantity of microbes at a specific body site
FMT	Fecal microbiota transplantation; refers to the placement of donor fecal content into gastrointestinal tract of recipient
Germ-free	A host animal that carries no microorganisms
Gnotobiotic	A host animal that carries a defined set of microorganisms, either synthetically implanted or transferred from another host; often used to refer to model organisms with humanized microbiota
Metagenome	The total genomic DNA of all organisms within a community
Metagenomics	The study of uncultured microbial communities, typically relying on high-throughput experimental data and bioinformatic techniques
Metametabolome	The total metabolite pool (and possibly fluxes) of a community
Metaproteome	The total proteome of all organisms within a community
Metatranscriptome	The total transcribed RNA pool of all organisms within a community
Microbiome	The total microbial community and biomolecules within a defined environment
Microbiota	The total collection of microbial organisms within a community, typically used in reference to an animal host
Microflora	An older term used synonymously with "microbiota"
Ortholog	A homologous gene in two species distinguished only by a speciation event; in practice, used to denote any gene sufficiently homologous as to represent strong evidence for conserved biologic function
Prebiotic	A food substance metabolized by the microbiota so as to directly or indirectly benefit the host
Probiotic	A live microorganism consumed by the host with direct or indirect health benefits
16S rRNA	The transcribed form of the 16S ribosomal subunit gene, the smaller RNA component of the prokaryotic ribosome, used as the most common taxonomic marker for microbial communities
Analysis Terms	
Alpha diversity	Within-sample taxonomic diversity
Beta diversity	Between-sample taxonomic diversity
Binning	Assignment of sequences to taxonomic units
Chimera	An artificial DNA sequence generated during amplification, consisting of a combination of two (or more) true underlying sequences
Functional metagenomics	Computational or experimental analysis of a microbial community with respect to the biochemical and other biomolecular activities encoded by its composite genome
Gap filling	The process of imputing missing or inaccurate gene abundances in a set of pathways
OTU	Operational taxonomic unit; a cluster of organisms similar at the sequence level beyond some threshold (e.g., 95%) used in place of species, genus, and so on
WGS	Whole-genome shotgun; used to describe shotgun sequencing of individual organisms and, sometimes, microbial communities, although this is not completely accurate because no "whole genome" is typically involved
WMS	Whole-metagenome shotgun; used in reference to undirected metagenomic sequencing to distinguish it from sequencing directed toward specific taxonomic marker genes

of vaginal versus cesarean birth on the developing infant microbiome, the impact of mode of delivery on microbial composition and function remains unclear.

In addition, maternal factors, such as the indication for cesarean, use of preincision versus perioperative antibiotics, consumption of probiotics, maternal body mass index (BMI), and gestational diabetes status, are understudied likely modifiers.[11,99,101,115] These observations have been summarized in reviews by several investigative teams, and formed part of the basis for the American College of Obstetricians and Gynecologists (ACOG) Committee Opinion on "vaginal seeding".[19,36,87,116,117]

ORAL MICROBIOME

The oral microbiome is diverse and abundant. Although a significant amount of research has focused on the gut microbiome with respect to health and disease, there is a substantial body of work regarding the oral microbiome. The HMP demonstrated exquisite niche specificity within the oral microbiome, with distinct communities observed at the level of taxa and gene carriage patterns (Figs. 2.1 and 2.2). To put this into perspective, 1 mL of human saliva in a healthy adult contains approximately 100 million cells, which are discrete from the community of the surrounding oral microbiome. Several studies[2,3,118–121] have documented the unanticipated robustness of the oral microbiome. Microarray, early pyrosequencing, and culture methodologies estimated approximately 700 oral microbial phylotypes. However, dental plaque sampling pooled from 98 healthy adults was estimated to represent 22 phyla comprising 3621 and 6888 species-level phylotypes in the saliva and plaque, respectively.[118] The HMP estimated nearly 70 distinct genera in the same human specimen types.[2] The most abundant bacterial genera in healthy adults include *Actinomyces, Bacteroides, Prevotella, Streptococcus, Fusobacterium, Lautropia, Leptotrichia, Corynebacterium, Veillonella, Rothia, Capnocytophaga, Selenomonas,* and *Treponema,* and the TM7 lineage. In addition to the bacterial kingdom, *Methanobrevibacter*

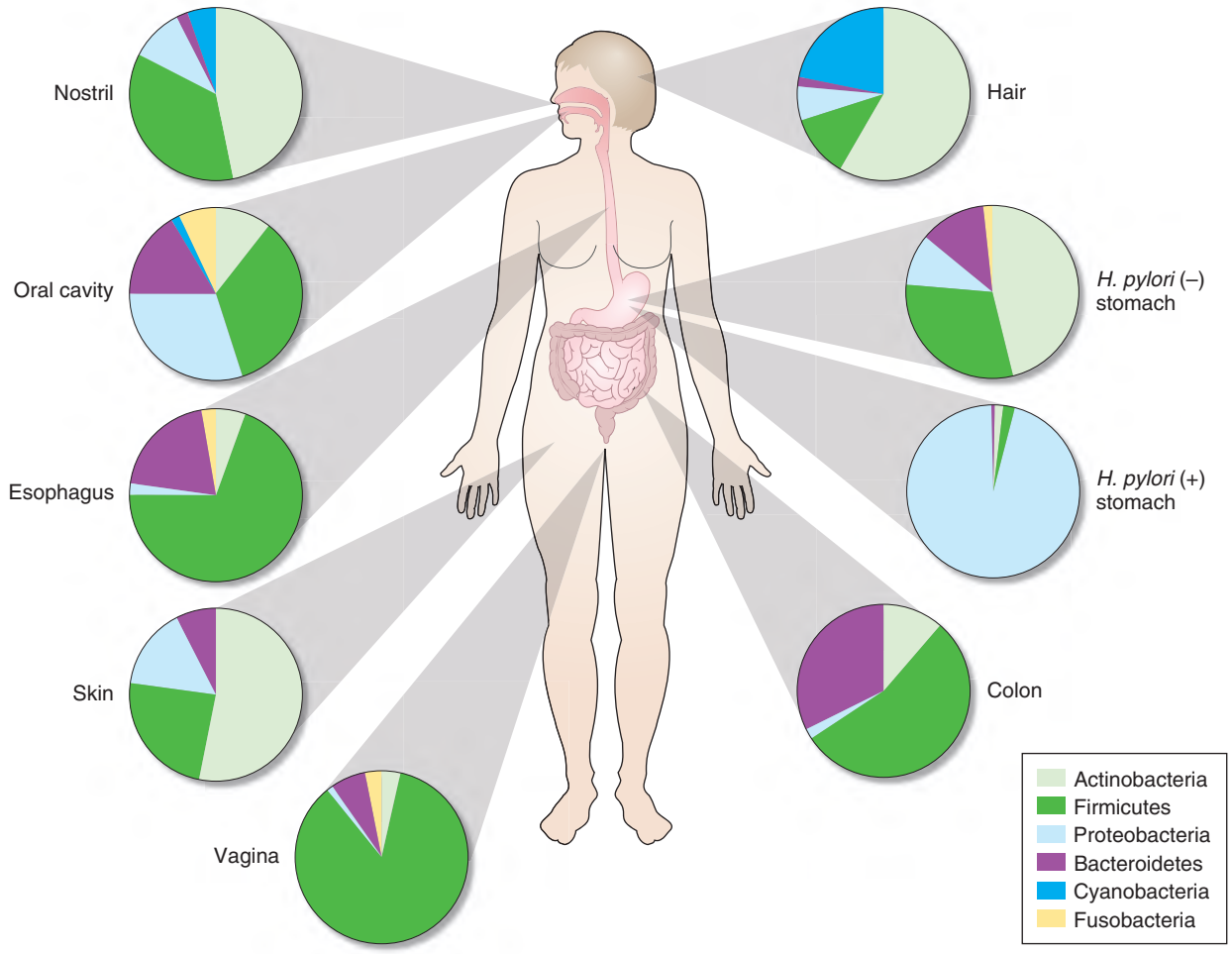

FIG. 2.2 Compositional differences in the microbiome by anatomic site. Metagenomic massively parallel sequencing approaches have demonstrated exquisite body site specificity, and higher level (e.g., phylum) taxonomic features display temporal (longitudinal) stability in individuals at specific anatomic sites. Represented in the figure are relative distributions (percentages) of taxa projected at the phylum level. *(Modified from Cho I, Blaser MJ. The human microbiome: at the interface of health and disease.* Nat Rev Genet. *2012;13:260–270.)*

spp. from the Archaea domain was also identified in the oral microbiome.

Interindividual variation in the microbiome is richly observed in the oral niche. For example, *Streptococcus* spp. dominate the oropharynx,[2,6] with exquisite strain-level genomic variation within microbial species and enriched for host-specific structural variants around genomic islands. Abundant *Streptococcus* phages were found to co-occur with many *Streptococcus* species in the oral cavity, contributing further to interindividual variation.[6] Although these differences are also observed in the gut and skin (leading to issues such as methicillin-resistant *S. aureus* [MRSA]), the oral microbiome is unique in its maintenance of closely adjacent subsites within the niche. The tonsil microbiome can be distinguished from the tongue, and the tongue from the palate. These differences are evident despite spatial proximity and constant contact between these sites.

Associations Between Oral Microbiota and Disease States

With maintenance of niche and subsite specificity in mind, it is not surprising that long-standing associations have been documented between oral health and disease manifestations in distal body sites. For example, periodontal disease is the most common infectious disease affecting the teeth. Left untreated or ineffectively treated, periodontitis is a known independent predictor of, and comorbid contributor to, preterm birth, cardiovascular disease, pulmonary disorders, diabetes, and obesity.[122] Additional strong correlations between the qualitative composition of the oral microbiota as a whole have been made with different disease states. The generation of the dental plaque biofilm that we experience daily has been well characterized.[118–121,122] A succession of early and late colonizing species, dominated early by *Streptococcus* spp., coat the dentin surface of the tooth. Once this early biofilm has been established, a series of highly coevolved oral bacterial and host interactions occur to likely layer bacteria on bacteria, which ultimately generates a large and diverse microbiota load on the tooth surface with a generally healthy periodontium (see Table 2.1). Novel structures of oral microbial communities have been characterized such as "hedgehogs" and "cauliflowers." Oral "hedgehogs" contain filamentous, anaerobic bacteria such as *Corynebacterium, Leptotrichia,* and *Fusobacterium* at the base, while aerobes such as *Streptococcus* and *Haemophilus* are found in the periphery.[123] The presence of *Streptococcus* in oral "hedgehogs" creates a lactate-rich, low-oxygen environment that is hospitable to *Fusobacterium* and *Leptotrichia*.[11] Perhaps these structures contribute to plaque-based oral pathogenesis by enabling oral pathogens to persist and proliferate in the oral cavity. The spatial distributions of microbes within human-associated communities are being unraveled, and highlight the nature of microbe-microbe interactions at body surfaces. A deeper appreciation of the microbial community structures and biofilms may lead to key insights in terms of pathology and treatment.

Periodontitis may be considered akin to bacterial vaginosis (BV) or inflammatory bowel disease (IBD) because it is not the singular absence or presence of a given species or subgenus that drives the oral gum inflammation. Rather, the complexity of the subgingival microbiota and biofilm establishment promote a model of a microbial community-associated disease. In one recent study using deep sequencing,

periodontitis was associated with a shift to populations enriched with gram-negative genera such as *Catonella, Haemophilus,* and *Tannerella*.[121] The microbiome-minded clinician scientist will consider the stability of oral microbiome composition as a hallmark of human health. One exception is infection by *Aggregatibacter actinomycetemcomitans* because this gram-negative rod appears to cause a highly aggressive periodontitis (localized aggressive periodontitis) in Africans with strong host tropism.[122] Other investigators have used whole-genome shotgun sequencing in smaller-scale studies to suggest a potential role for uncultured bacteria of the TM7 lineage in other forms of periodontitis, but broader health and disease associations have yet to be tested in a population-based cohort.

SKIN AND NASOPHARYNX

Because the integument (including skin, hair, and nails) that comprises the main body surface is in constant contact with the outside environment, the human skin consists of diverse sets of local habitats and niches for the human microbiome. The human skin comprises various ecosystems that differ markedly by relative differences in temperature, humidity, and glandular distribution. The human skin microbiome and the nature of the local environment can vary greatly depending on anatomic location. One report described bacterial compositional differences in 20 different sites on the human skin.[124] Recent studies have demonstrated that the skin microbiome differs among healthy individuals more than any other site.[2,3] Bacterial communities are composed largely of transient (superficial), autochthonous (deep surface), and adherent microbes lying adjacent to the epidermis, but they have also been detected in the subepidermal compartment including the dermis and dermal adipose tissue.[125]

Different factors contribute to variation of the human skin microbiome. These factors include host physiology (sex, age, site); environment (local climate, geographic location); immune system; host genotype; lifestyle (occupation, hygiene); and pathobiology (skin and systemic diseases).[107] Different regions of the human skin contain characteristic distributions of different types of glands. These glands produce oily substances such as sebum and other lipid, carbohydrate, and proteinaceous components that may serve as nutrients for the microbiome, and as inhibitors to particular classes of microbes. For example, sebaceous gland–rich regions include the head, shoulders, upper arms, and upper torso.[124,126] Eccrine glands are most abundant in the crown of the head, under the arms, and on the palmar surfaces of the hands. Apocrine glands are enriched around the eyes and ears, nipples, and genital regions. Relative humidity is another key factor affecting microbial composition of the skin. Areas rich in sebaceous glands are enriched for *Propionibacterium* spp. (now called *Cutibacterium* spp.), whereas moist and dry skin areas are enriched for *Corynebacterium* spp. and Betaproteobacteria, respectively (Fig. 2.3).[107,124]

Sebaceous sites contain microbial communities with the least species diversity, whereas dry skin sites house microbial communities with more compositional richness and evenness.[107]

The HMP provided the most comprehensive survey of the human skin microbiome in terms of the number of different male and female adult individuals.[2] A total of 242 individuals were fully analyzed at three body sites (anterior nares, antecubital fossa, retroauricular crease). This study confirmed that the skin microbiome is distinct from that of other body sites and is characterized by an intermediate degree of alpha diversity and richness per specimen. The phyla Actinobacteria, Firmicutes, and Verrucomicrobia were the dominant groups in the human skin,[127] in contrast with the predominance of Bacteroidetes, Firmicutes, and Proteobacteria in the human gut. Therefore even at the level of phyla composed of hundreds of different bacterial species, stark differences are evident in the skin compared with other body sites.[128] Results depend on technical considerations and different specimen types such as skin swabs, blade scrapings, and skin biopsy specimens.[129] Age is an important factor as evidenced by shifts in bacterial communities that occur during the sexual maturation process.[130] Corynebacteriaceae and Propionibacteriaceae predominated in Tanner 5 individuals compared with Tanner 1 children.

Specific groups of microbes may be conserved in the skin of healthy individuals, whereas interindividual variation may account for differences in relative abundances of microbes and differences in disease susceptibilities.[107] Different proportions of *Propionibacterium* spp. and Betaproteobacteria, for example, may be present on the backs or arms, respectively, in different individuals, but these bacterial groups are present in the majority of healthy individuals at these body sites. Representative bacterial genera in the human skin across sites include *Corynebacterium, Eubacterium, Propionibacterium, Staphylococcus,* and *Streptococcus*,[127] and the fungal *Malassezia* spp.[131] In the nares, *Corynebacterium* is the most common bacterial genus,[107] and persistent *S. aureus* colonization was found in the nares in 24% of healthy human subjects.[132] The nasal microbiota contains different proportions of staphylococci, with some individuals carrying mostly *S. aureus* and some individuals carrying mostly *Staphylococcus epidermidis.* The genus *Malassezia* is the predominant fungal genus of the human skin at multiple body sites, including the head, torso, arms, and legs,[127] except for sites on the foot.[131] Persistent effects of antifungal agents on skin fungi or "mycome" were observed in this study.[131]

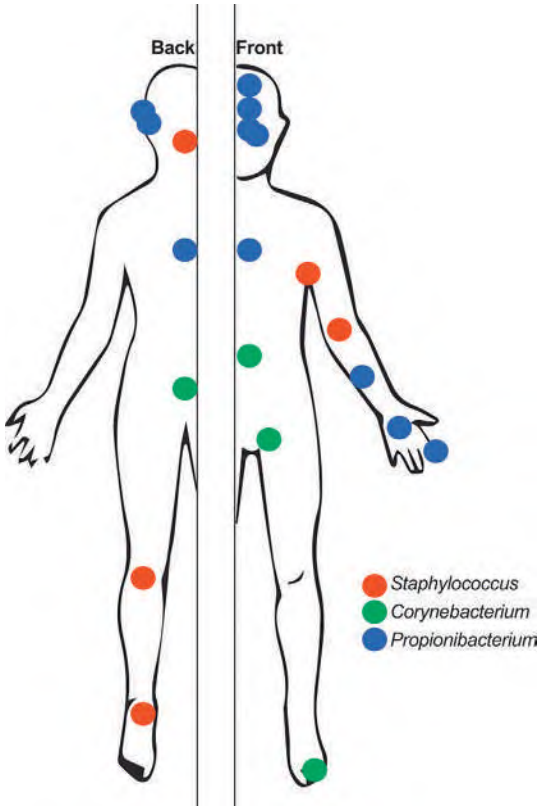

FIG. 2.3 Predominant microbes in specific skin sites. This schematic figure shows the predominant bacterial genera (by color) at each skin site on the human body. *(From Grice EA. The intersection of microbiome and host at the skin interface: genomic- and metagenomic-based insights.* Genome Res. *2015;25:1514–1520.)*

Relative distributions of commensal bacteria and opportunistic pathogens may help explain different patterns of cutaneous infections and systemic penetration of pathogens from skin surfaces. Hospitalized individuals with *S. aureus*–predominant nasal microbiomes were also more likely to carry MRSA associated with their hospitalizations.[133] In cases of atopic dermatitis, staphylococci including *S. aureus* and *S. epidermidis* populations appear to "bloom" and contribute to disease flares and relapse at specific skin sites.[134] With respect to acne, only *Cutibacterium acnes* (formerly *Propionibacterium acnes*) strains belonging to one of six ribotypes were associated with acne, whereas nonpathogenic *C. acnes* strains belonging to other ribotypes were not associated with disease.[135,136]

Bacterial composition of the human skin may be useful for forensic applications. One study described the utility of skin fingertip microbiome patterns for tracking the use of keyboards and perhaps other devices by specific individuals.[137] This study highlights the individualized nature

of the skin microbiome at specific sites and the fact that interindividual differences in bacterial composition may help explain relative disease susceptibilities.

AIRWAY AND PULMONARY MICROBIOME

Human lungs were once believed to be sterile, but innovative research and advances in DNA sequencing technology have provided evidence of microbial communities in upper and lower airways. The airway microbiome has now been characterized on the first day of life, with a predominance of Firmicutes and Proteobacteria noted.[138] When comparing extremely low-birth-weight (ELBW) preterm infants delivered vaginally with ELBW preterm infants delivered via cesarean section, no significant differences were seen in the communities isolated from tracheal aspirates.[139]

Specimens from different sites along the respiratory tract of six healthy adults were characterized to determine which specimen types were most appropriate for microbiome research.[140] Specimen types ranged from nasopharyngeal swabs to bronchoalveolar lavages (BALs). Microbial composition of lung communities appeared consistent among the various sampling sites, and diminished amounts of bacterial DNA content were isolated from deeper lung specimens. The microbiomes of the healthy, lower respiratory tract (BAL specimens) in healthy adults were composed mainly of Firmicutes and Bacteroidetes with a predominance of Veillonellaceae, Prevotellaceae, and Streptococcaceae. A subsequent study attempted to characterize the fungal communities in BAL specimens obtained from healthy individuals, and although few fungal sequences were obtained, common environmental organisms such as Davidiellaceae, *Cladosporium,* and *Aspergillus* were identified in low abundance.[141] More recently, protected specimen brushings and BAL specimens were obtained from eight healthy adults, and the findings suggested that bacterial communities detected in the lower airways were distinct from potential contaminants, with *Prevotella, Veillonella,* and *Streptococcus* as the most abundant genera in the lower airway microbiome.[142]

Staphylococcus carriage and subsequent infection in hospitalized patients was the topic of a separate study comparing nasal swabs in a healthy cohort and a cohort of hospitalized patients.[140] Although Actinobacteria (68%) and Firmicutes (27%) were the most common phyla in nasal swabs of healthy patients, a reversal in relative abundance was reported for the hospitalized cohort with Firmicutes (71%) and Actinobacteria (20%). This significant shift in community composition was attributed to an overall increase in the amount of *S. aureus* and *S. epidermidis,* and to reduced amounts of *P. acnes* in the hospitalized groups. As mentioned previously, disease states are generally associated with diminished bacterial diversity, but the contrary was found in a recent study in a subset of patients with pulmonary tuberculosis (TB). Sputum specimens collected from healthy individuals and patients with TB suggested greater bacterial diversity in the TB group compared with the healthy group.[143] At the phylum level, Firmicutes, Bacteroidetes, Proteobacteria, and Actinobacteria were detected as expected in the healthy group. The TB group indicated a decrease in Bacteroidetes and an increase in Firmicutes and Actinobacteria. Predominant genera were similar across both groups with the most common bacteria identified as *Streptococcus, Granulicatella, Actinomyces, Prevotella,* and *Veillonella.* Several genera were found only in the TB group, suggesting that the lungs of patients with TB may harbor unique bacterial species.

A comparison of children with persistent bacterial bronchitis (PBB) and healthy children revealed decreased bacterial diversity in the lungs of children with PBB versus healthy children.[144] Discrepancies were seen between the dominant organisms identified by sequencing and culture results, with only 15 of 24 patients (62.5%) producing a positive culture for the organism that was predominant in the pulmonary microbiome. *Haemophilus, Neisseria, Streptococcus,* and *Moraxella* were each shown to dominate microbial communities of patients with PBB.

Bacterial and viral pathogens have been implicated as possible causes of asthma and potential triggers of asthmatic episodes. In a study of healthy children and children with asthma, significant shifts in overall bacterial communities present in the respiratory tract were not detected at the phylum level, with both groups displaying the expected predominance of Bacteroidetes, Firmicutes, and Proteobacteria (the asthma group exhibited a slightly different order of prevalence: Firmicutes, Proteobacteria, and Bacteroidetes).[145] Interesting to note, although the healthy children were characterized by carrying *Prevotella, Streptococcus, Veillonella,* and *Fusobacterium,* the asthmatic group included increased relative abundance of *Haemophilus,* a pathogen *(Haemophilus influenzae)* previously implicated as a potential trigger of asthmatic episodes. In a more recent study focusing on severe asthma, multiple genera, most notably *Bacteroides*, *Faecalibacterium*, and *Roseburia*, were significantly increased in children with severe asthma compared with those without asthma.[146] Adding to the microbiome data in the asthma population is a compelling study from Ecuador, where treatment of respiratory illnesses differs greatly from the standard of care in the United States. Oropharyngeal swabs were obtained from both wheezing and healthy infants, and all patients had minimal exposure to antibiotics and no exposure to inhaled steroids.[147] The overall bacterial community in the study population consisted of Firmicutes, Proteobacteria, Actinobacteria, Bacteroidetes, and Fusobacteria in order of predominance. The most common genera isolated were consistent with the findings of Hilty and colleagues,[145] with most bacteria identified as *Streptococcus, Veillonella, Atopobium,* and *Prevotella.* In the wheezing group, a greater frequency of *Neisseria, Prevotella, Corynebacterium, Staphylococcus, Actinomyces,* and *Haemophilus* was detected.[147]

The airways of patients with cystic fibrosis (CF) provide an ideal environment for bacterial proliferation leading to chronic and acute respiratory infections characteristic of the disease. In the general CF population, a diverse bacterial community has been found in respiratory specimens from younger patients with mild disease and good lung function, and decreased bacterial diversity has been found, as expected, in older patients with more severe disease and significant declines in lung function.[148–150] Microbiome-based studies have also confirmed that anaerobic bacteria are far more prevalent in patients with CF than indicated by routine culture detection. Cox and colleagues[148] conducted a PhyloChip-based study in both children and adults with CF in 2010. The results suggested that bacterial diversity in the pulmonary microbiomes of children with CF increased until approximately age 11 and continuously decreased during adulthood.[148] A core pulmonary microbiome has been suggested in CF, consisting of seven genera: *Pseudomonas, Streptococcus, Neisseria, Catonella, Porphyromonas, Prevotella,* and *Veillonella.*[151] *Pseudomonas aeruginosa* was the most prevalent bacterium identified in this adult cohort. Although limited data exist on fungal communities of the airways, *Candida, Aspergillus, Geotrichum,* and *Malassezia* spp. were commonly identified in the sputa of patients with CF.[152]

In a study of healthy subjects versus subjects with CF, the CF group was found to have an increased amount of Proteobacteria and Actinobacteria with a relative reduction in Bacteroidetes and complete loss of Fusobacteria.[149] Reduced bacterial diversity in the airways was confirmed in the CF specimens, with 17 different phyla identified in the healthy population compared with 10 different phyla identified in the CF population. Decreased bacterial diversity in patients with CF has repeatedly been associated with advanced disease, and increased amounts of *P. aeruginosa*.[150] In contrast, the relative abundance of *Streptococcus* spp. has been associated with increased bacterial diversity and relative clinical stability or lack of evidence of worsening of the disease phenotype in patients.[153] Longitudinal analysis confirmed the presence of airway microbial communities with decreasing diversity in children with CF and advancing age. The presence of bacterial pathogens was also associated with increased inflammation of the lower airways.[154]

Intubated patients are at risk for a variety of additional health complications including ventilator-associated pneumonia (VAP). Microbiome characterization of tracheal aspirates obtained from intubated and mechanically ventilated intensive care unit (ICU) patients showed that increased duration of mechanical ventilation and subsequent development of VAP were associated with decreased bacterial diversity.[155] Antibiotic administration was not shown to affect diversity in this cohort. A separate study compared subjects with respiratory failure requiring intubation and mechanical ventilation with healthy subjects undergoing bronchoscopy.[156] Bacterial diversity was reported in the ventilated subjects,

and diversity continued to decrease with extended time on the ventilator. Several microbiomes were dominated by a single microorganism, and pathogens identified via culture correlated with the most abundant DNA sequences in these cases. In two cases, specific pathogens were identified via sequencing and yielded clinically actionable information, in parallel with negative cultures. As another example of disease-specific microbial perturbations in the airways, alterations in the human airway microbiome may contribute to the development of lung disease (e.g., bronchopulmonary dysplasia).[140]

Connections among microbiomes in different body sites may help us understand patterns of human infections. An innovative study by Madan and colleagues[157] sought to characterize and compare gastrointestinal and respiratory tract specimens from infants with CF during the first 24 months of life. Overall, *Veillonella* and *Streptococcus* were most commonly identified among both specimen types. *Streptococcus, Veillonella,* and *Prevotella* were the most prevalent genera in the respiratory tract, and *Bacteroides, Bifidobacterium,* and *Veillonella* were the most prevalent genera in the gastrointestinal tract. In general, bacterial diversity increased over time, with more rapid diversification occurring in the developing respiratory tract. Interesting to note, gut colonization preceded subsequent respiratory colonization for several genera, including *Roseburia, Dorea, Sporacetigenium, Coprococcus, Blautia, Enterococcus,* and *Escherichia.* Aspiration may account for the spread of organisms from the gut to the airways, possibly resulting in infections in the compromised host.

GASTROINTESTINAL TRACT

Esophagus

The proximal esophagus and midesophagus are thought to mostly harbor transient bacteria and yeasts, and little is known about the nature of microbial communities at these locations. Microbes in these locations mostly originate from the oropharynx owing to swallowing or the stomach owing to reflux. Contributions of the microbiome to proximal esophagitis remains an open question. Relative susceptibilities to bacterial, fungal, and viral infections of the proximal and midesophagus may be affected by such transient microbial communities.

By contrast, the distal esophagus immediately cephalic to the gastroesophageal sphincter contains a moderately diverse microbiome. This esophageal region appears to harbor a collection of permanent residents that include bacteria, yeasts, and viruses in human patients. Older culture-based studies showed that gram-positive bacteria such as *Streptococcus* dominated the distal esophageal ecosystem. More recent studies pertaining to the HMP have generated comprehensive data sets based on 16S rRNA gene sequencing and whole-metagenome sequencing. In terms of global parameters, the distal esophageal microbiome is less rich and less diverse than that of the large intestine. The phenotypically normal distal esophagus contains a less complex microbiome composed largely of the phylum Firmicutes and dominated by the genus *Streptococcus.*[158,159]

In contrast with the large intestine, it appears that relative "overgrowth" and increased microbial diversity in the esophagus are associated with disease states. To explain these findings, we propose the microbial diversity setpoint hypothesis. This hypothesis states that increased diversity in regions that usually have lesser diversity is associated with disease and inflammation, and that reduced diversity in regions of greater diversity is associated with disease and inflammation. Increased bacterial species richness and diversity in the esophagus were associated with esophagitis and Barrett's esophagus.[159] The distal esophagus in patients with esophagitis or Barrett's esophagus contained a diverse microbiome dominated by gram-negative anaerobes and microaerobes,[159] and this population shift may explain the greater propensity toward inflammation in patients exposed to greater concentrations of endotoxin or lipopolysaccharides (LPSs) in the distal esophagus.[159] Qualitative aspects of bacterial composition, in addition to quantitative features, may contribute to host susceptibility to esophageal infections and esophagitis.

Stomach

Discovery of *Helicobacter pylori* in 1982 led to the widespread appreciation of bacterial colonization in the human stomach. Follow-up studies highlighted the differential abundance of *H. pylori* in different regions of the stomach, with the greatest concentration of bacteria generally present in the antrum. Recognition of the widespread prevalence of *H. pylori* in diverse human populations and evolutionary studies tracing patterns of human migration[160] emphasized its potential significance as a commensal bacterium that coevolved with man during thousands of years of human evolution. Blaser and colleagues[161] first proposed that *H. pylori* may represent an important commensal microbe in the human stomach, and its presence was protective against gastroesophageal reflux disease (GERD), Barrett's esophagus, and adenocarcinomas of the gastric cardia and distal esophagus. In summary, these discussions laid the foundation for concepts of the human microbiome and how antibiotics could increase chronic disease risk by extermination of valuable members of the human gastrointestinal microbiome.

More recent studies based on 16S rRNA gene sequencing demonstrated the presence of 128 bacterial phylotypes in human gastric biopsy specimens.[162] The dominant species was *H. pylori* in infected individuals, but this bacterial species did not affect the overall bacterial composition in a series of 19 subjects. The dominant phyla in the human stomach, such as Bacteroidetes, Firmicutes, Proteobacteria, and Actinobacteria, overlap with those of the large intestine, but the phylum Fusobacteria seems to be differentially enriched in the stomach. An interesting finding was the presence of *Deinococcus*-like organisms in the stomach, undefined at the time of publication.

A more recent gastric microbiome study highlighted the ecologic importance of *H. pylori* and the presence of communities composed of different microbes.[163] Gram-positive bacteria such as *Streptococcus* and *Lactobacillus* spp. were found in the human stomach. When *H. pylori* is absent, the genus *Streptococcus* is the predominant genus in the gastric microbiome.[163] Differences in gastric bacterial communities, in the presence of *H. pylori*, may predispose patients to acute or chronic gastritis, intestinal metaplasia, and gastric adenocarcinoma.[164] The inability to maintain a sufficiently low luminal pH in conditions such as achlorhydria or proton pump inhibitor consumption has been associated with relative bacterial "overgrowth" and increased bacterial diversity associated with chronic disease states including gastric cancer.[165] In accordance with the microbial diversity setpoint hypothesis, the stomach is a region of limited bacterial diversity, so increased diversity would be predicted to be associated with inflammation and chronic disease. Regions with limited microbial diversity such as the esophagus, stomach, and proximal small intestine may also be more susceptible to pathogens including viruses that are able to survive and thrive in these ecosystems. Finally, the long-term effects on microbial gut composition after antibiotic therapy of *H. pylori* infection, including the diminution of Actinobacteria for weeks after treatment, highlight the potential risks of antimicrobial therapy.[166]

Intestine (Small and Large)

The biogeography of compartments in the small and large intestine affects bacterial composition and metabolic pathways present in the human microbiome. On the basis of older culture-based and more recent DNA sequencing–based studies, bacterial diversity gradually increases in a proximal-to-distal manner from the duodenum through the jejunum to the distal ileum and colon. The duodenum and jejunum can be considered areas of relatively limited microbial diversity, in contrast with the terminal ileum, which contains a rich and diverse microbiome similar to the proximal colon. Although substantial differences in microbial composition in different intestinal compartments are appreciated, detailed information is available only for the major compartments such as small intestine, large intestine (colon), and feces. Ileostomy specimens and small intestinal fluid specimens obtained with a nasoileal catheter provide glimpses into the composition and function of the small intestinal microbiome. The gram-positive Firmicutes phylum including genera such as *Streptococcus, Veillonella* (*Clostridium* cluster IX), and *Clostridium* (e.g., cluster XIVa) appear to dominate the small intestine,[167,168] in contrast with dominant bacterial groups in the colon. Other bacterial phyla such as Bacteroidetes and Proteobacteria (e.g., *E. coli* and other Gammaproteobacteria) were detected in relatively greater abundance in the distal small intestine. In active celiac disease, specific genera such as *Bacteroides, Clostridium,* and *Staphylococcus* are enriched in relative abundance.[158] Metagenomics and gene expression

profiling data show that dominant *Streptococcus* spp. express genes involved in carbohydrate metabolism and simple carbohydrate transport phosphotransferase systems (PTSs). Various intestinal bacterial species convert simple sugars into organic acids such as lactate, acetate, propionate, and butyrate, and ultimately affect the proliferation and virulence of various pathogens. For example, acetate produced by *Bifidobacterium* spp. suppresses the virulence of Shiga-like toxins produced by verotoxigenic *E. coli*.[169] The human gut virome contributes to the rapid evolution and microbiologic diversity in the intestine with implications for infectious diseases. Viruses such as the Microviridae (lytic phages) evolve rapidly in the intestine based on DNA substitution rates,[170] and viral populations undergo dramatic changes in the human gut during the first 2 years of life.[171] In terms of functional consequences, temperate phages that infect members of the Bacteroidetes phylum encode antibiotic resistance genes in the human intestinal microbiome.[172]

The large intestine (cecum; ascending, transverse, and descending colon; sigmoid and rectum) contains rich and highly diverse microbial communities with two predominant bacterial phyla in healthy individuals (Bacteroidetes and Firmicutes). The phylum Bacteroidetes is dominated by the genus *Bacteroides,* whereas the phylum Firmicutes contains diverse commensal microbes of genera such as *Clostridium, Faecalibacterium, Lactobacillus,* and *Ruminococcus*. The first week of life is highlighted by large-scale fluctuations in gut bacterial composition in neonates, and microbial succession patterns have been described in preterm infants with predictable increases in classes such as Gammaproteobacteria.[173,174] Multidrug-resistant enteric pathogens can become established in the neonatal gut microbiome and could predispose infants to difficult-to-treat enteric infections[17,173] By the end of the first 3 years of life, a relative equilibrium is reached with a diverse, adult-like gut microbiome.[109] Shifts in bacterial phyla, families, and genera occur throughout childhood. Genera such as *Bifidobacterium and Faecalibacterium* and microbial metabolic pathways such as vitamin B_{12} biosynthesis are enriched in healthy children versus healthy adults.[175,176] Major differences in gut microbial composition have been reported in different pediatric populations on three different continents.[177,178] In healthy adults, these phyla are less abundant with a proportionately greater predominance of the dominant phyla Bacteroidetes and Firmicutes. Notably, members of the genus *Bacteroides* have been associated with interindividual variation of the intestinal microbiome among healthy adults.[6] Genera such as *Bifidobacterium* gradually decline during adulthood. The Eldermet study[179] described shifts in the gut microbiome in elderly individuals, and bacterial composition depended on environmental factors such as type of residence (nursing homes versus community residence). Although the global importance of enterotypes remains controversial, bacterial DNA sequencing data from stool specimens indicated that healthy humans can be classified into three basic enterotypes (enriched for *Bacteroides, Prevotella,* or *Ruminococcus* in enterotypes 1, 2, and 3, respectively). The functional importance of these enterotypes and whether such microbiome "types" influence clinical outcomes remain unknown.

In regions of abundant microbial diversity such as the intestine, reduced diversity has been associated with increased disease susceptibility and disease relapse in the intestine. One example is the documented reduction in overall bacterial diversity in stool specimens from patients with recurrent *C. difficile* disease versus patients with single disease episodes.[180] IBD and necrotizing enterocolitis (NEC) are other disease phenotypes that have been associated with reductions in microbial richness and diversity in the intestine.[181] Reduced microbial diversity may contribute to diminished immunomodulatory functions by the microbiome and reduced resistance to intestinal pathogens, effectively predisposing the host to infectious enteritis or colitis.

Several well-established and potential pathogens belong to the enteric bacteria within the phylum Proteobacteria, a minority but prevalent phylum of the intestine. The class of Gammaproteobacteria includes pathogens belonging to the genera *Escherichia, Salmonella, Vibrio,* and *Yersinia*. Interesting to note, Gammaproteobacteria have been described in greater abundance in different disease conditions such as IBD, irritable bowel syndrome (IBS), and NEC.[182,183,184] Specific classes of bacteria such as Gammaproteobacteria may provoke inflammation by producing potent endotoxins or other molecules that exacerbate disease states. Acute or chronic disease states coupled with loss of integrity of the intestinal epithelial lining may predispose specific patients to colitis or abdominal infections.

Studies have largely depended on self-collected stool specimens, although numerous studies have documented findings in colonic biopsy specimens. Data from self-collected stool specimens appear to be a reasonably effective source of information about the distal intestinal microbiome, and these specimens have provided most of our current knowledge about the intestinal microbiome. Colonic biopsy specimens revealed the overlap in composition with stool, and differences in relative abundance and microheterogeneity present in different intestinal regions.[185] Largely on the basis of fecal data, intestinal bacterial composition, which represents the vast majority of microbial genetic content in the gut microbiome, is relatively stable in terms of composition and functional capacity within an individual. General surgical interventions, in addition to medications and diet, may profoundly alter the composition and function of the gut microbiome,[186,187] emphasizing that environment may be the dominant driver over host genetics when it comes to shaping the human microbiome.[188] A detailed short-term study examining the impact of diet on the microbiome confirmed that enterotypes were stable within a 10-day period even after major dietary changes such as introduction of high-fat, low-fiber or low-fat, high-fiber diets.[189] Although microbial composition may be relatively stable despite minor fluctuations within an individual, it appears that dietary changes including the introduction of probiotics may rapidly alter gene expression patterns in the gut microbiome. Data from mouse models[190] suggest that functional dynamism in terms of gene expression and microbial metabolomes may easily exceed the routine changes in intestinal microbial composition. Finally, resilience of the intestinal microbiome has been demonstrated by the nearly complete reconstitution of human gut bacteria within 4 weeks after cessation of oral antimicrobial therapy.[84] Such considerations of the relative dynamism and resilience may be important to consider in disease states with less diverse intestinal microbiomes, and these properties of the microbiome may be different in regions adjacent to the intestinal mucosa.

VAGINAL MICROBIOME

With use of traditional culture techniques and light microscopy, a preponderance of lactobacilli was first appreciated as comprising normal vaginal microbiota. In 1892, Gustav Döderlein described his discovery that the vagina was dominantly populated with *Lactobacillus* spp. Since that time, the notion that lactic acid– and hydrogen peroxide–producing lactobacilli are the keystone genera in a healthy vagina has led to the commonly accepted notion that *Lactobacillus* spp. stability and dominance are the hallmarks of a "healthy" vagina and are central to reproductive health. In the late 1800s, Menge and Kronig first described the isolation of anaerobes in addition to *Lactobacillus* from the vagina, often with a dearth of lactobacilli. In other cohorts of women, "abnormal microbes" were observed because of their association with a malodorous discharge, dominated by *Gardnerella vaginalis* and later ascribed as "bacterial vaginosis" (BV). A symbiotic relationship exists between the vaginal microbiota and each host that likely provides the host protection from colonization by harmful pathogens.[191] Molecular studies of the vaginal microbiome in healthy reproductive-aged women confirmed earlier observations demonstrating domination by *Lactobacillus* spp., producing lactic acid to lower the vaginal pH.[192] Species such as *Lactobacillus crispatus* and *Lactobacillus iners* are the most abundant vaginal bacterial species in the absence of BV, and *Eggerthella* and *Leptotrichia* species dominated the vaginal microbiome in the presence of BV.[193] Among smaller cohorts of equally healthy women, molecular interrogations have demonstrated that their vaginal microbiome is alternately dominated by a diverse array of anaerobic microorganisms.[192] Some studies hypothesize that the composition of these communities can be correlated with disturbance responses in the vagina.[192]

Bacterial Vaginosis: An Example of a Prevalent Pathobiont in the Vaginal Microbiome

The clinical diagnosis of BV is familiar to any medical student during training and includes vaginal secretions with a pH level greater than 4.5, a "fishy" odor best elicited by mixing vaginal secretions with 10% potassium hydroxide (KOH) solution, a milky white vaginal discharge,