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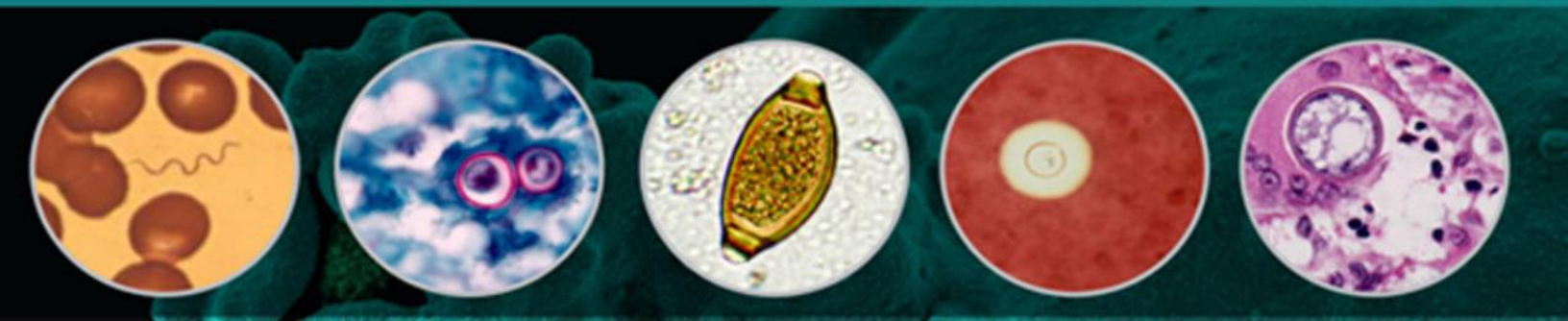
# Principles and Practice of Infectious Diseases



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# Principles and Practice of Infectious Diseases


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*Orthopoxviruses: Vaccinia (Smallpox Vaccine), Variola (Smallpox), Monkeypox, and Cowpox*
*Other Poxviruses That Infect Humans: Parapoxviruses (Including Orf Virus), Molluscum Contagiosum, and Yatapoxviruses*

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*Infections in Patients With Spinal Cord Injury*

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*Infections in Asplenic Patients*

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Histoplasma capsulatum *(Histoplasmosis)*

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*Classification of Streptococci*

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*Epidemiology and Prevention of AIDS and HIV Infection, Including Preexposure Prophylaxis and HIV Vaccine Development*

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*Granulocytic Phagocytes*

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*Sinusitis*

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*Biology of Viruses and Viral Diseases*

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*Diagnosis of Human Immunodeficiency Virus Infection*

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*Introduction to Ectoparasitic Diseases*
*Lice (Pediculosis)*
*Scabies*
*Myiasis and Tungiasis*
*Mites, Including Chiggers*
*Ticks, Including Tick Paralysis*

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*Innate (General or Nonspecific) Host Defense Mechanisms*

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*Viral Hepatitis*
*Antiviral Drugs Against Hepatitis Viruses*

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*Ertapenem, Imipenem, Meropenem, Doripenem, and Aztreonam*
*Penicillins and β-Lactamase Inhibitors*

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*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*

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*Linezolid, Tedizolid, and Other Oxazolidinones*

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Clostridioides difficile (*Formerly* Clostridium difficile) *Infection*

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*Rotaviruses*

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Rickettsia typhi *(Murine Typhus)*
Ehrlichia chaffeensis *(Human Monocytotropic Ehrlichiosis),* Anaplasma phagocytophilum *(Human Granulocytotropic Anaplasmosis), and Other Anaplasmataceae*

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*Leprosy* (Mycobacterium leprae)

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*Bacillary Dysentery:* Shigella *and Enteroinvasive* Escherichia coli

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*Prevention of Infective Endocarditis*

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*Endophthalmitis*
*Introduction to Eye Infections*
*Periocular Infections*
*Infectious Causes of Uveitis*

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*Prevention of Infective Endocarditis*

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*Legionnaires' Disease and Pontiac Fever*

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Candida *Species*

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Streptococcus agalactiae *(Group B Streptococci)*

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*Acute Pneumonia*

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*Innate (General or Nonspecific) Host Defense Mechanisms*

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*Flaviviruses (Dengue, Yellow Fever, Japanese Encephalitis, West Nile Encephalitis, Usutu Encephalitis, St. Louis Encephalitis, Tick-Borne Encephalitis, Kyasanur Forest Disease, Alkhurma Hemorrhagic Fever, Zika)*

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*Chronic Fatigue Syndrome (Systemic Exertion Intolerance Disease)*

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*Respiratory Syncytial Virus*

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*Brucellosis (*Brucella *Species)*

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*Mucosal Immunity*

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*Malaria* (Plasmodium *Species*)

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*Tapeworms (Cestodes)*

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*A Molecular Perspective of Microbial Pathogenicity*

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*Human Metapneumovirus*

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*The Immunology of Human Immunodeficiency Virus Infection*

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Bacillus *Species and Related Genera Other Than* Bacillus anthracis

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Staphylococcus epidermidis *and Other Coagulase-Negative Staphylococci*

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*Vesicular Stomatitis Virus and Related Vesiculoviruses (Chandipura Virus)*

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Mycobacterium tuberculosis

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*Pharyngitis*

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Rickettsia akari *(Rickettsialpox)*

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*Endocarditis and Intravascular Infections*

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*Infections in Returning Travelers*
*Protection of Travelers*

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Bacillus anthracis *(Anthrax)*

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*Coccidioidomycosis* (Coccidioides *Species*)

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*Evaluation of the Patient With Suspected Immunodeficiency*

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*Human Immunodeficiency Viruses*

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*Human Immunodeficiency Virus Infection in Women*

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*Diseases Caused by* Clostridium
Bacteroides, Prevotella, Porphyromonas, *and* Fusobacterium *Species (and Other Medically Important Anaerobic Gram-Negative Bacilli)*

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*Blastomycosis*

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*Brain Abscess*

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*Marburg and Ebola Virus Hemorrhagic Fevers*

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Babesia *Species*

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*Topical Antibacterials*

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Clostridioides difficile (*Formerly* Clostridium difficile) *Infection*

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*Rubella Virus (German Measles)*
*Measles Virus (Rubeola)*

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*Infections in Asplenic Patients*

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*Microbial Keratitis*

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*Outpatient Parenteral Antimicrobial Therapy*

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*Bites*

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*Paracoccidioidomycosis*

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*Esophagitis*

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*Fusidic Acid*

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Stenotrophomonas maltophilia *and* Burkholderia cepacia *Complex*

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*Enterobacteriaceae*

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*Antimycobacterial Agents*

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*Diarrhea With Little or No Fever*
*Acute Dysentery Syndromes (Diarrhea With Fever)*

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*Brucellosis* (Brucella *Species)*

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Leptospira *Species (Leptospirosis)*

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Mycobacterium tuberculosis

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*Infections in Solid-Organ Transplant Recipients*

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*Microbial Keratitis*

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Bordetella pertussis

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Chlamydia pneumoniae

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Entamoeba *Species, Including Amebic Colitis and Liver Abscess*

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*Syndromes of Enteric Infection*
*Typhoid Fever, Paratyphoid Fever, and Typhoidal Fevers*

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Coxiella burnetii *(Q Fever)*

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*Approach to the Patient With Central Nervous System Infection*
*Acute Meningitis*

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*Hepatitis B Virus*
*Hepatitis Delta Virus*

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*Dermatophytosis (Ringworm) and Other Superficial Mycoses*

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*Infections Caused by Percutaneous Intravascular Devices*

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*Infections in Older Adults*

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*Human Genetics and Infection*

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Acinetobacter *Species*

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*Prevention of Infective Endocarditis*

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*Cell-Mediated Defense Against Infection*

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*Evaluation of the Patient With Suspected Immunodeficiency*

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*Endocarditis and Intravascular Infections*

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Mycoplasma pneumoniae *and Atypical Pneumonia*

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*Quinolones*

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*Urinary Tract Agents: Nitrofurantoin, Fosfomycin, and Methenamine*
*Relapsing Fever Caused by* Borrelia *Species*

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*Agents of Mycetoma*
*Uncommon Fungi and Related Species*

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Campylobacter jejuni *and Related Species*

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*Parainfluenza Viruses*

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*Nonsuppurative Poststreptococcal Sequelae: Rheumatic Fever and Glomerulonephritis*

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Streptococcus pneumoniae

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Listeria monocytogenes

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*The Acutely Ill Patient With Fever and Rash*

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*Health Care–Acquired Hepatitis*

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*Anaerobic Infections: General Concepts*

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*Polymyxins (Polymyxin B and Colistin)*

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*Emerging and Reemerging Infectious Disease Threats*

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*Other Coryneform Bacteria,* Arcanobacterium haemolyticum, *and Rhodococci*

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*Tapeworms (Cestodes)*

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*Agents of African Trypanosomiasis (Sleeping Sickness)*
*Drugs for Protozoal Infections Other Than Malaria*
Trypanosoma *Species (American Trypanosomiasis, Chagas Disease): Biology of Trypanosomes*

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Campylobacter jejuni *and Related Species*

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*Mucosal Immunity*

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*Blastomycosis*

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*Nosocomial Pneumonia*

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*Prosthetic Valve Endocarditis*

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*Myocarditis and Pericarditis*

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Bartonella, *Including Cat-Scratch Disease*

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*Chlamydia pneumoniae*

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*Anaerobic Cocci and Anaerobic Gram-Positive Nonsporulating Bacilli*

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*Agents of Mucormycosis and Entomophthoramycosis*

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*JC, BK, and Other Polyomaviruses: Progressive Multifocal Leukoencephalopathy (PML)*
*Neurologic Diseases Caused by Human Immunodeficiency Virus Type 1 and Opportunistic Infections*

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*Introduction to Protozoal Diseases*

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*Free-Living Amebae*

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Toxoplasma gondii

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*Immunization*

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*Transfusion- and Transplantation-Transmitted Infections*

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*Microbial Conjunctivitis*

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*Antibiotic Allergy*

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*Syndromes of Enteric Infection*

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*Outpatient Parenteral Antimicrobial Therapy*

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Mycoplasma pneumoniae *and Atypical Pneumonia*

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*Aminoglycosides*

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*Cephalosporins*

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Leptospira *Species (Leptospirosis)*

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*Infections in Injection Drug Users*

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*Peritonitis and Intraperitoneal Abscesses*

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*Emerging and Reemerging Infectious Disease Threats*

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*Agents of Mucormycosis and Entomophthoramycosis*

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*Immunomodulators*

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*Acute Dysentery Syndromes (Diarrhea With Fever)*

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*Infections in Solid-Organ Transplant Recipients*

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Candida *Species*
*Cell-Mediated Defense Against Infection*

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*Zoonoses*

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*Mumps Virus*

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

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*Other Gram-Negative and Gram-Variable Bacilli*

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*Antimicrobial Stewardship*

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Nocardia *Species*

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*Appendicitis*
*Splenic Abscess*
*Infections of the Liver and Biliary System (Liver Abscess, Cholangitis, Cholecystitis)*
*Diverticulitis and Neutropenic Enterocolitis*

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Leishmania *Species: Visceral (Kala-Azar), Cutaneous, and Mucosal Leishmaniasis*

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*Introduction to Helminth Infections*
*Trematodes (Schistosomes and Liver, Intestinal, and Lung Flukes)*

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*Diagnosis of Human Immunodeficiency Virus Infection*

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*Alphaviruses (Chikungunya, Eastern Equine Encephalitis)*

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Neisseria gonorrhoeae *(Gonorrhea)*

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Coxiella burnetii *(Q Fever)*

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*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*

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Bacillus anthracis *(Anthrax)*


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*Cystic Fibrosis*

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*Rifamycins*

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*Management of Opportunistic Infections Associated With Human Immunodeficiency Virus Infection*

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*Immunization*

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*Sulfonamides and Trimethoprim; Trimethoprim-Sulfamethoxazole*

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*Antimalarial Drugs*
*Drugs for Helminths*
*Drugs for Protozoal Infections Other Than Malaria*

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*Vulvovaginitis and Cervicitis*

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*Prostatitis, Epididymitis, and Orchitis*

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*Coronaviruses, Including Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS)*

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*Plague* (Yersinia pestis)

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*Intestinal Nematodes (Roundworms)*

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*Rat-Bite Fever:* Streptobacillus moniliformis *and* Spirillum minus

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*Emerging and Reemerging Infectious Disease Threats*

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*Prophylaxis and Empirical Therapy of Infection in Cancer Patients*

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Pneumocystis *Species*

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Salmonella *Species*

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Enterococcus *Species,* Streptococcus gallolyticus *Group, and* Leuconostoc *Species*

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*Tetracyclines, Glycylcyclines, and Chloramphenicol*

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*The Immunology of Human Immunodeficiency Virus Infection*

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Toxoplasma gondii

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Entamoeba *Species, Including Amebic Colitis and Liver Abscess*

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*Drugs for Helminths*

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Staphylococcus aureus *(Including Staphylococcal Toxic Shock Syndrome)*

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*Antiviral Agents: General Principles*

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*Human Illness Associated With Harmful Algal Blooms*

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*Daptomycin and Quinupristin-Dalfopristin*

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*Human T-Cell Leukemia Viruses (HTLV-1, HTLV-2)*

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Moraxella catarrhalis, Kingella, *and Other Gram-Negative Cocci*
Haemophilus *Species, Including* H. influenzae *and* H. ducreyi *(Chancroid)*

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*Daptomycin and Quinupristin-Dalfopristin*
*Glycopeptides (Vancomycin and Teicoplanin) and Lipoglycopeptides (Telavancin, Oritavancin, and Dalbavancin)*
Enterococcus *Species,* Streptococcus gallolyticus *Group, and* Leuconostoc *Species*

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*Burns*

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Streptococcus pneumoniae

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Listeria monocytogenes

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*Metronidazole*

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*Hepatitis C*

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*Glycopeptides (Vancomycin and Teicoplanin) and Lipoglycopeptides (Telavancin, Oritavancin, and Dalbavancin)*

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Giardia lamblia
*Visceral Larva Migrans and Other Uncommon Helminth Infections*

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*Granulocytic Phagocytes*

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*Epiglottitis*

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*Other Pathogenic Vibrios*

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*Enterobacteriaceae*

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*Bacterial Lung Abscess*

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*Macrolides and Clindamycin*

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*Antifungal Drugs: Echinocandins*

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*Topical Antibacterials*

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*Infectious Arthritis of Native Joints*

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Sporothrix schenckii
*Bacillary Dysentery:* Shigella *and Enteroinvasive* Escherichia coli

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*Diseases Caused by* Clostridium
Bacteroides, Prevotella, Porphyromonas, *and* Fusobacterium *Species (and Other Medically Important Anaerobic Gram-Negative Bacilli)*

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*Molecular Mechanisms of Antibiotic Resistance in Bacteria*

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*Myocarditis and Pericarditis*

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*Immunomodulators*

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*Tables of Antiinfective Agent Pharmacology*
*Pharmacokinetics and Pharmacodynamics of Antiinfective Agents*

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Orientia tsutsugamushi *(Scrub Typhus)*

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*Bacterial Lung Abscess*

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*Pleural Effusion and Empyema*

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*Cellulitis, Necrotizing Fasciitis, and Subcutaneous Tissue Infections*
*Myositis and Myonecrosis*
*Lymphadenitis and Lymphangitis*

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*The Clinician and the Microbiology Laboratory: Test Ordering, Specimen Collection, and Result Interpretation*

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Aspergillus *Species*

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*Microbial Keratitis*
*Microbial Conjunctivitis*

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Francisella tularensis *(Tularemia)*

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*Cryptococcosis* (Cryptococcus neoformans *and* Cryptococcus gattii)

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*Other Poxviruses That Infect Humans: Parapoxviruses (Including Orf Virus), Molluscum Contagiosum, and Yatapoxviruses*

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*Introduction to Protozoal Diseases*
Entamoeba *Species, Including Amebic Colitis and Liver Abscess*

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*Introduction to Bacteria and Bacterial Diseases*

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*Nutrition, Immunity, and Infection*

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*Molecular Mechanisms of Antibiotic Resistance in Bacteria*

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*Rifamycins*

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*Designing and Interpreting Clinical Studies in Infectious Diseases*

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*Antimalarial Drugs*

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Staphylococcus aureus *(Including Staphylococcal Toxic Shock Syndrome)*

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*Syphilis* (Treponema pallidum)

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*Complement and Deficiencies*

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*A Molecular Perspective of Microbial Pathogenicity*

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

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*Introduction to Protozoal Diseases*

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*Other Coryneform Bacteria,* Arcanobacterium haemolyticum, *and Rhodococci*
Erysipelothrix rhusiopathiae

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*Nutrition, Immunity, and Infection*

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*Human Immunodeficiency Viruses*

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*A Molecular Perspective of Microbial Pathogenicity*

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Klebsiella granulomatis *(Donovanosis, Granuloma Inguinale)*

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*Paracoccidioidomycosis*

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Sporothrix schenckii

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*Adenoviruses*

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*Hyperbaric Oxygen*

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*Temperature Regulation and the Pathogenesis of Fever*

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*Poliovirus*
*Parechoviruses*
*Coxsackieviruses, Echoviruses, and Numbered Enteroviruses (EV-A71, EVD-68, EVD-70)*
*Introduction to the Human Enteroviruses and Parechoviruses*

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Bartonella, *Including Cat-Scratch Disease*

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*Emerging and Reemerging Infectious Disease Threats*

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*Flaviviruses (Dengue, Yellow Fever, Japanese Encephalitis, West Nile Encephalitis, Usutu Encephalitis, St. Louis Encephalitis, Tick-Borne Encephalitis, Kyasanur Forest Disease, Alkhurma Hemorrhagic Fever, Zika)*

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*Legionnaires' Disease and Pontiac Fever*

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*Classification of Streptococci*

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*Mediastinitis*
Staphylococcus epidermidis *and Other Coagulase-Negative Staphylococci*

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*Rabies (Rhabdoviruses)*

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*Agents of Actinomycosis*

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*Disinfection, Sterilization, and Control of Hospital Waste*

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*Typhoid Fever, Paratyphoid Fever, and Typhoidal Fevers*
Vibrio cholerae

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*Temperature Regulation and the Pathogenesis of Fever*

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*Syphilis* (Treponema pallidum)

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Corynebacterium diphtheriae *(Diphtheria)*

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*Hyperbaric Oxygen*

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*Myocarditis and Pericarditis*

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*Pulmonary Manifestations of Human Immunodeficiency Virus Infection*

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*Herpes Simplex Virus*

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*Psittacosis* (*Due to* Chlamydia psittaci)

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*Whipple Disease*

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Trichomonas vaginalis

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*Prebiotics, Probiotics, and Synbiotics*

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*Acute Exacerbations of Chronic Obstructive Pulmonary Disease*

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*Orthopedic Implant–Associated Infections*

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*Health Care–Acquired Hepatitis*

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*Lymphocytic Choriomeningitis Virus, Lassa Virus, and the South American Hemorrhagic Fevers (Arenaviruses)*

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*Nonsuppurative Poststreptococcal Sequelae: Rheumatic Fever and Glomerulonephritis*

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*Neurologic Diseases Caused by Human Immunodeficiency Virus Type 1 and Opportunistic Infections*

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*Appendicitis*
*Infections of the Liver and Biliary System (Liver Abscess, Cholangitis, Cholecystitis)*
*Diverticulitis and Neutropenic Enterocolitis*

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Mycoplasma pneumoniae *and Atypical Pneumonia*

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*Diagnosis of Human Immunodeficiency Virus Infection*

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*Infections in Solid-Organ Transplant Recipients*

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*Free-Living Amebae*

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Pneumocystis *Species*

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*Urinary Tract Infections*

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*Infections of Nonvalvular Cardiovascular Devices*

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Nocardia *Species*

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*Principles of Antiinfective Therapy*

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*Osteomyelitis*

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*Lyme Disease (Lyme Borreliosis) Due to* Borrelia burgdorferi

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*Other Gram-Negative and Gram-Variable Bacilli*

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Neisseria meningitidis

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*Adenoviruses*

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*General Clinical Manifestations of Human Immunodeficiency Virus Infection (Including Acute Retroviral Syndrome and Oral, Cutaneous, Renal, Ocular, Metabolic, and Cardiac Diseases)*
Mycobacterium tuberculosis

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*Antifungal Agents: Amphotericin B*

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Streptococcus pyogenes

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Klebsiella granulomatis *(Donovanosis, Granuloma Inguinale)*

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*Quinolones*

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Streptococcus anginosus *Group*

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Mycobacterium avium *Complex*

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Cyclospora cayetanensis, Cystoisospora belli, Sarcocystis *Species*, Balantidium coli, *and* Blastocystis *Species*

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*Gastrointestinal, Hepatobiliary, and Pancreatic Manifestations of Human Immunodeficiency Virus Infection*

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*Cellulitis, Necrotizing Fasciitis, and Subcutaneous Tissue Infections*

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*Topical Antibacterials*

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*Surgical Site Infections and Antimicrobial Prophylaxis*

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*JC, BK, and Other Polyomaviruses: Progressive Multifocal Leukoencephalopathy (PML)*

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Chlamydia trachomatis *(Trachoma and Urogenital Infections)*

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*Osteomyelitis*

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*Hepatitis B Virus*
*Hepatitis Delta Virus*

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*Flaviviruses (Dengue, Yellow Fever, Japanese Encephalitis, West Nile Encephalitis, Usutu Encephalitis, St. Louis Encephalitis, Tick-Borne Encephalitis, Kyasanur Forest Disease, Alkhurma Hemorrhagic Fever, Zika)*

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Aspergillus *Species*
*Antifungal Drugs: Azole*

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*Zoonotic Paramyxoviruses: Nipah, Hendra, and Menangle Viruses*

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*Paracoccidioidomycosis*

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*Innate (General or Nonspecific) Host Defense Mechanisms*
*Syphilis* (Treponema pallidum)

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*Health Care–Associated Urinary Tract Infections*

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*Astroviruses and Picobirnaviruses*
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*Noroviruses and Sapoviruses (Caliciviruses)*

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*Hepatitis E Virus*

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*Fusidic Acid*

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*Antiretroviral Therapy for Human Immunodeficiency Virus Infection*


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*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*

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*Encephalitis*
*Orthoreoviruses and Orbiviruses*
*Coltiviruses*
*Prions and Prion Disease of the Central Nervous System (Transmissible Neurodegenerative Diseases)*

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*Cystic Fibrosis*

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*Infections in Recipients of Hematopoietic Stem Cell Transplants*

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*Infections in the Immunocompromised Host: General Principles*

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*Mediastinitis*

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Babesia *Species*

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*Hepatitis A Virus*

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

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*Parechoviruses*

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*Prophylaxis and Empirical Therapy of Infection in Cancer Patients*

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Vibrio cholerae

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*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*

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*Antimycobacterial Agents*
*Infections Caused by Nontuberculous Mycobacteria Other Than* Mycobacterium avium *Complex*

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*Acute Bronchitis*
*Respiratory Syncytial Virus*

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*Miscellaneous Antiviral Agents (Interferons, Tecovirimat, Imiquimod, Pocapavir, Pleconaril)*

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Pneumocystis *Species*

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*Tropical Sprue and Environmental Enteric Dysfunction*

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*Tropical Sprue and Environmental Enteric Dysfunction*

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*Rat-Bite Fever:* Streptobacillus moniliformis *and* Spirillum minus

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Bordetella pertussis

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Yersinia enterocolitica *and* Yersinia pseudotuberculosis

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Nocardia *Species*

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*Disinfection, Sterilization, and Control of Hospital Waste*

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*Pediatric Human Immunodeficiency Virus Infection*

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*Malaria* (Plasmodium *Species*)

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# 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.

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# 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*<br>*Ruminococcus bromii*<br>*Bacteroides ovatus*<br>*Akkermansia muciniphila*<br>*Streptococcus sanguinis*<br>*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*<br>*Mycobacterium leprae*<br>*Treponema pallidum*<br>*Neisseria gonorrhoeae*<br>*Shigella dysenteriae*<br>*Salmonella* Typhi<br>*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*<br>*Streptococcus pyogenes*<br>*Streptococcus pneumoniae*<br>*Neisseria meningitidis*<br>*Haemophilus influenzae*<br>*Helicobacter pylori*<br>*B. fragilis*<br>*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*<br>*Francisella tularensis*<br>*Borrelia burgdorferi*<br>*Bacillus anthracis*<br>*Brucella abortus*<br>*Mycobacterium bovis*<br>*Mycobacterium leprae*<br>*Salmonella enterica*<br>*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*<br>*Clostridium botulinum*<br>*Burkholderia pseudomallei*<br>*Mycobacterium marinum*<br>*Mycobacterium avium*<br>*Pseudomonas aeruginosa*<br>*Legionella pneumophila*<br>*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*<br>*fur* | Temperature<br>Iron concentration | Pyelonephritis-associated pili<br>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<br>*virF* | Temperature, calcium<br>Temperature | Secretion of effector proteins<br>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]

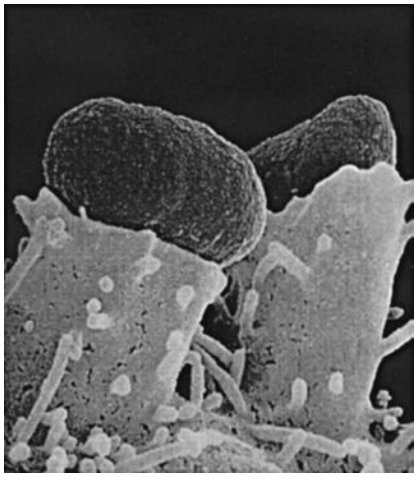

**FIG. 1.1 Scanning electron micrograph depicting pseudopod, or "pedestal," formation by enteropathogenic *escherichia coli* (EPEC) as it interacts with the surface of an epithelial cell.** This form of intimate adherence requires a bacterial adhesin, intimin; a receptor of bacterial origin, Tir, that 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.

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*The complete reference list is available online at Expert Consult.*


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

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## 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

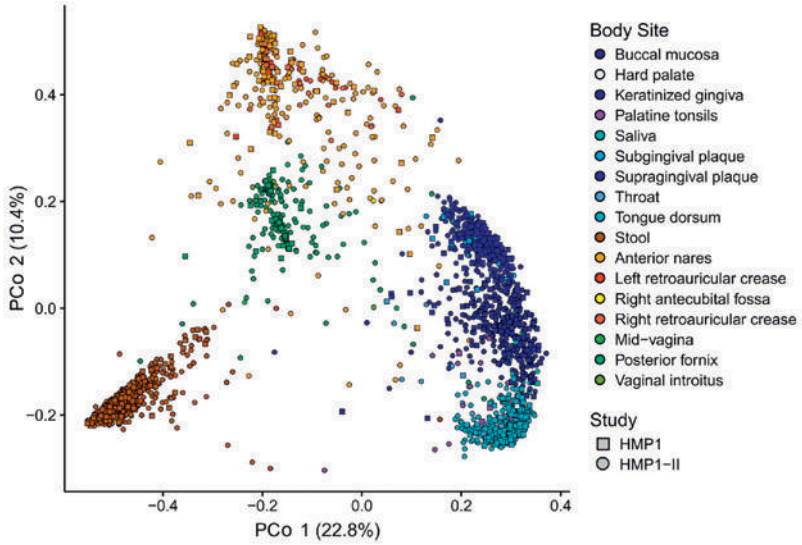


**FIG. 2.1 The human microbiome is composed of distinct bacterial populations at different body sites.** This principal components *(PCo)* analysis plot shows each distinct body site (indicated by distinct colors) and its microbial composition in healthy adults. Each colored circle in space represents 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