1 Introduction to Medical Microbiology

Historical Perspective

Imagine the excitement felt by the Dutch biologist Anton van Leeuwenhoek in 1674 as he peered through his carefully ground microscopic lenses at a drop of water and discovered a world of millions of tiny "animalcules." Almost 100 years later, the Danish biologist Otto Müller extended van Leeuwenhoek's studies and organized bacteria into genera and species according to the classification methods of Carolus Linnaeus. This was the beginning of the taxonomic classification of microbes. In 1840 the German pathologist Friedrich Henle proposed criteria for proving that microorganisms were responsible for causing human disease (the "germ theory" of disease). Robert Koch and Louis Pasteur confirmed this theory in the 1870s and 1880s with a series of elegant experiments proving that microorganisms were responsible for causing anthrax, rabies, plague, cholera, and tuberculosis. Other brilliant scientists proved that a diverse collection of microbes was responsible for causing human disease. The era of chemotherapy began in 1910, when the German chemist Paul Ehrlich discovered the first antibacterial agent, which was a compound effective against the spirochete that causes syphilis. This was followed by Alexander Fleming's discovery of penicillin in 1928, Gerhard Domagk's discovery of sulfanilamide in 1935, and Selman Waksman's discovery of streptomycin in 1943. In 1946 the American microbiologist John Enders was the first to cultivate viruses in cell cultures, leading the way to the large-scale production of virus cultures for vaccine development. Thousands of scientists have followed these pioneers, each building on the foundation established by their predecessors and each adding an observation that expanded our understanding of microbes and their role in disease.

Our knowledge and practice of microbiology are undergoing a remarkable transformation driven by the rapid technological advances in genome analysis. The techniques developed in the Human Genome Project and Human Microbiome Project moved into the clinical laboratory, enabling simple and inexpensive diagnostic tests for the rapid detection and identification of organisms. Previously unappreciated insights about the pathogenic properties of organisms, functional attributes of the endogenous flora, and taxonomic relationships were also revealed. The complexity of the medical microbiology we know today rivals the limits of the imagination. There are thousands of different types of microbes that live in and on us, some of which cause serious human diseases but most of which are important for the metabolic and immunologic functions of healthy humans. To understand this information and organize it in a useful manner, it is important to understand some of the basic aspects of medical microbiology. To start, microbes responsible for human disease can be subdivided into the following four general groups: viruses, bacteria, fungi, and parasites, with each having its own level of complexity.

Viruses

Viruses are the smallest infectious particles, ranging in diameter from 18 to 600 nm (most viruses are <200 nm and cannot be seen with a light microscope). The genome of human viruses consists of either deoxyribonucleic acid or ribonucleic acid. The viral nucleic acids required for replication are enclosed in a protein shell with or without a lipid envelope. Viruses are true parasites, requiring host cells for replication. The cells they infect and the host response to the infection dictate the nature of the clinical disease. More than 2000 species of viruses have been described, with approximately 650 infecting humans and animals. Infection can lead either to rapid replication and destruction of the cell or to a long-term chronic relationship with possible integration of the viral genetic information into the host genome. The factors that determine which of these takes place are only partially understood.

A viral disease can range from the relatively benign common cold to life-threatening Ebola, from acute disease to chronic presentations, and even infections that progress to cancer. The immune response provides both protection and pathology, and in many viral infections may be the primary cause of illness. Often initiated with nonspecific flu-like symptoms caused by host responses to the virus, a viral disease is characterized by the specific tissue(s) infected by the virus (e.g., central nervous system, pulmonary, gastrointestinal). Classic symptomatology guides diagnosis by viral isolation in cell culture or detection of viral nucleic acids or antigens by molecular- and immunologic-based tests. Treatment has also advanced, including a tolerable cure for hepatitis C virus and lifelong control of human immunodeficiency virus infections. New vaccines have reduced or effectively eliminated the risk for several virus infections, and vaccines for human papillomavirus and hepatitis B virus are also preventing cancers.

Bacteria

Bacteria are deceptively simple in structure. They are **prokaryotic** organisms, which are simple unicellular organisms with no nuclear membrane, mitochondria, Golgi bodies, or endoplasmic reticulum, that reproduce by asexual division. Most bacteria have either a Gram-positive cell wall with a thick peptidoglycan layer or a Gram-negative cell wall with a thin peptidoglycan layer and an overlying outer membrane. Some bacteria lack this cell wall structure and compensate by surviving only inside host cells or in a hypertonic environment. The size (1–20 μm or larger), shape (spheres, rods, or spirals), and spatial arrangement (single cells, chains, or clusters) are used for the preliminary classification of bacteria, and the phenotypic and genotypic properties of the bacteria form the basis for the definitive classification.

We live in a microbial world with microbes in the air we breathe, the water we drink, and the food we eat, many of which are relatively avirulent but some of which are capable of producing life-threatening diseases. Bacterial disease can result from the toxic effects of bacterial products (e.g., toxins) or when bacteria invade normally sterile body tissues and fluids. Some bacteria are always pathogenic expressing virulence factors that cause tissue damage, others cause disease by stimulating inflammation, and many bacteria do both. Proper identification of the infecting bacteria allows for prediction of the disease course and appropriate antimicrobial therapy. Unfortunately, inappropriate use of antimicrobials and other factors have led to the selection of multiply antimicrobial-resistant bacteria that cannot be treated.

Fungi

In contrast to bacteria, the cellular structure of fungi is more complex. These are **eukaryotic** organisms that contain a well-defined nucleus, mitochondria, Golgi bodies, and endoplasmic reticulum. Fungi can exist either in a unicellular form **(yeast)**, that can replicate asexually, or in a filamentous form **(mold)**, that can replicate asexually and sexually. Some fungi have a mold form in the environment and a yeast or spherical form in the body at 37°C. These are known as **dimorphic** fungi and include *Histoplasma, Blastomyces, Coccidiodes*, and *Sporothrix*.

Fungal infections range from benign skin infections to life-threatening sepsis, pneumonia, meningitis, and disfiguring diseases. Most fungi are effectively controlled by host immunity and can reside peacefully within an individual for a lifetime, but these same fungi can cause serious disease in the immunocompromised host. Antimicrobial therapies can disrupt the unique metabolic pathways and structures of the fungi but may also require lengthy treatments or be toxic to the host. As with bacteria, extensive use of antifungal agents in the hospital setting has resulted in the emergence of yeasts and molds that express intrinsic and acquired resistance to several different classes of antifungal agents.

Parasites

Parasites are the most complex microbes. Although all parasites are classified as eukaryotic, some are unicellular and others are multicellular. They range in size from tiny protozoa as small as 4 to 5 μm in diameter (the size of some bacteria) to tapeworms that can measure up to 10 m in length and arthropods (bugs). Indeed, considering the size of some of these parasites, it is hard to imagine how these organisms came to be classified as microbes. Their life cycles are equally complex, with some parasites establishing a permanent relationship with humans and others going through a series of developmental stages in a progression of hosts. One of the difficulties confronting students is the need to not only understand the spectrum of diseases caused by parasites but also the epidemiology of these infections because this is critical for developing a differential diagnosis. Helpful hints are obtained from the travel and dietary history of the patient because many parasites are unique to different global regions. Therapies currently exist for most parasites, but the development of resistance to antiparasitic agents complicates the treatment of many infections.

Immunology

It is difficult to discuss human microbiology without also discussing the innate and adapted immune responses to the microbes. Physical barriers and our endogenous microbial population limit invasion by microbes, while the immune system activates local defenses. Specific adapted immune responses target invading microbes for elimination and block their toxins. Unfortunately, the immune response is often too late or too slow to prevent or limit the spread of the infection. The ensuing war between the host protections and microbial invaders escalates and, even when successful, the inflammatory response that results often contributes to or may be the cause of the symptoms of the disease. To improve the human body's ability to prevent infection, the immune system can be augmented either through the passive transfer of antibodies present in immunoglobulin preparations or through active immunization with components of the microbes (vaccines). Ultimately, the innate and adapted immune responses are the best prevention and cure for microbial disease.

Diagnostic Microbiology

The clinical microbiology laboratory plays an important role in the diagnosis and control of infectious diseases. Newer molecular, proteomic, and immunologic technologies are being used to enhance the information that the laboratory can provide. Many diagnostic tests require viable samples, and the quality of the results depends on the quality of the specimen collected from the patient, how it is transported from the patient to the laboratory, and the techniques used to demonstrate the microbe in the sample. In addition, the collected specimen must be representative of the site of infection and not contaminated during collection with other organisms that colonize skin and mucosal surfaces. Comprehensive antimicrobial susceptibility determinations require viable and representative microbes purified from the clinical sample. The procedures for genome and antigen analysis have become less expensive and available for more pathogens, and these procedures may not require viable samples. These assays are very sensitive and specific and can enable previously unattainable rapid diagnoses.

Microbiology and Immunology in the Clinic

Relatively few organisms are classified as always pathogenic (e.g., rabies virus, *Bacillus anthracis*, *Shigella*, *Sporothrix schenckii*), whereas some establish disease only under well-defined circumstances or under certain conditions (e.g., opportunistic infections of immunocompromised individuals). Some diseases arise when a person is exposed to organisms from external sources, which is called an **exogenous infection** (e.g., influenza virus, *Clostridium tetani*, *Neisseria*

Box 1.1 Four Questions Regarding an Infectious Disease Patient

1. Is it an infection?
2. Where is the infection?
3. Which organism is causing the infection, and how is it causing the disease?
4. Should it be treated and, if so, what is the best treatment?

gonorrhoeae, *Coccidioides immitis*, and *Entamoeba histolytica*), but most human diseases are produced by organisms from the person's own microbial population that spread from normally colonized sites to sterile body sites (e.g., blood, brain, lungs, peritoneal cavity) in which disease can ensue **(endogenous infections)**. Some infections cause a single well-defined disease, which is often caused by the action of a virulence factor, such as a toxin (e.g., *C. tetani* [tetanus]), whereas others can cause several manifestations of disease (e.g., *Staphylococcus aureus* causes endocarditis, pneumonia, wound infections, food poisoning). The same disease can also be caused by different microbes (e.g., meningitis can be caused by viruses, bacteria, fungi, and parasites).

By understanding the characteristics of the microbe and the host's response to infection, a Sherlock Holmes–like approach can be applied to the microbial villain to solve the clinical infectious disease case. In addition, proper precautions can be taken to protect oneself and others from infection, and a sensible approach to prescribing appropriate therapy can be designed. When approaching a patient with an infectious disease, four questions must be answered (Box 1.1).

Question 1 and the first step in treating an infectious disease is—**is** this an infection? Infections are often accompanied by fever, inflammation, swollen lymph nodes, and other symptoms. Many of these disease presentations are caused by the inflammatory response to the infection, and these same presentations can be induced by other noninfectious disease syndromes.

The next question is, **where** is the infection? Knowing the site of infection can provide clues as to the possible microbes causing the infection and is important in picking an antimicrobial that can reach the infected tissue or site in an active form.

The answers to Question 3 are the main subjects of this book: **which** microbe is causing the infection and **how** is it causing the disease? Although the distinction between bacterial, viral, fungal, and parasitic infections can oftentimes be made from the history and physical presentations of the patient, certain laboratory tests can help focus the diagnosis. In addition to knowing the most appropriate test for a microbe or microbial syndrome, it is also important to know the limitations, sensitivity, and specificity of the tests. Once a differential diagnosis (a list of most probable villains) is obtained, then confirmatory tests can identify the disease-causing microbe.

The fourth question should take considerable thought: **should** the microbe be treated and, if so, what is the best treatment? Designing appropriate therapy is necessary for those infections that do not resolve on their own. Although necessary, antibiotic treatment can disrupt the normal flora and the immunologic and metabolic functions it performs. Proper therapy requires getting enough of the right antimicrobial drug to a susceptible pathogen at the site of infection. The antimicrobial potency, spectrum of activity, and pharmacologic properties of the drug are determined by the structure and mode of action of the drug. Pathogens may be naturally resistant, mutate, or acquire genetic information to make them resistant, and those that are resistant to antibiotics will be selected and will endure. Initial antimicrobial choices may attempt to cover all possible pathogens, but on the identification of the responsible microbe and its antimicrobial susceptibilities, antibiotics that are more specific, less expensive, easier to administer, and with fewer side effects should be prescribed. Proper **antimicrobial stewardship** will reduce costs, side effects, and potential development of resistant strains.

In addition to the four questions relating to the patient, the care provider must also know how to protect themselves and others from infection. Key questions include: Is there a vaccine? What safety precautions should be taken? How can hands and contaminated surfaces be disinfected? The best means to protect an individual from infection is to prevent exposure or contact, and the second best means is to be immunized against the microbe, by prior infection or vaccine.

Summary

It is important to realize that our knowledge of the microbial world is evolving continually. Just as the early microbiologists built their discoveries on the foundations established by their predecessors, present and future generations will continue to discover new microbes, new diseases, and new therapies. The following chapters are intended as a foundation of knowledge that can be used to build your understanding of microbes and their diseases.

2 Human Microbiome in Health and Disease

The human fetus lives in a remarkably protected environment; however, this rapidly changes as the infant is exposed to bacteria, fungi, and viruses from the mother, other close contacts, and the environment. Over the next few years, communities of microbes (**microbiota** or **normal flora** [Table 2.1]) form on the surfaces of the skin, nares, oral cavity, intestines, and genitourinary tract. The focus of this chapter is to gain an understanding of the role of these communities in the metabolic and immunologic functions of healthy individuals, factors regulating the composition of these communities, and how disruption of these communities can result in disease states.

Human Microbiome Project

Our current knowledge of the **microbiome** is rooted in the successful completion of the Human Genome Project, that was a 13-year international effort initiated in 1990 that determined the sequences of the approximately 3 billion nucleotides that make up the 23,000 protein-encoding genes in human deoxyribonucleic acid (DNA). Much like efforts to send a man to the moon, the greatest legacy of this work was the development of technologies that allow the generation and analysis of tremendous amounts of DNA and ribonucleic acid (RNA) sequencing data.

The Human Genome Project was followed by the Human Microbiome Project, which was a 5-year multinational study to analyze the genetic and metabolic composition of the microbial populations that live in and on healthy adults **(microbiome)**. To put the complexity of this program into perspective, it is estimated that bacterial cells outnumber human cells in the host and the bacterial population contributes at least 300-fold more unique protein genes.

The Human Microbiome Project was launched in 2007 with a collection of samples from the nose, mouth, skin, gut, and vagina from healthy adult volunteers. The microbes were identified by sequencing targeted regions of the 16S ribosomal RNA gene, and information about the gene content of the entire population was determined by sequencing the entire genome of a subset of microbes in selected specimens. These analyses showed that there is substantial variation in the species and gene composition for individuals and at different body sites. For example, bacteria colonizing the gut are different from those in the mouth, skin, and other body sites. These differences are greater than individual differences at a specific body site. The body site with the greatest taxonomic and genetic diversity was the intestine, and the vagina was the least complex. Microenvironments such as different regions of the mouth, gut, skin surface, and vagina also had their own unique microbiome (Fig. 2.1).

Core Microbiome

Most individuals share a **core microbiome**, arbitrarily defined as the species that are present at a specific site in 95% or more of individuals. The greatest numbers of shared species are present in the mouth, followed by the nose, intestine, and skin, and the fewest shared species are found in the vagina. Additionally, the small numbers of species that comprise the core microbiome are the most

Table 2.1 Glossary of Terms

Term	Definition
Microbiota	Community of microbes that live in and on an individual; can vary substantially between environmental sites and host niches in health and disease
Normal flora	Microbiota
Microbiome	Aggregate collection of microbial genomes in the microbiota
Core microbiome	Commonly shared microbial species among individuals at specific body sites; although typically represented by a limited number of species, these comprise the largest proportion of the microbial population
Secondary microbiome	Microbial species that contribute to the unique diversity of individuals at specific body sites; typically present in proportionately small numbers
Functional redundancy	Required functions (e.g., metabolism of nutrients, regulation of the immune response) that are provided by the diverse members of the microbiota
Taxonomic diversity	Diverse number of species that comprise the microbiota
Proteomics	Study of the protein products of the microbiome population
Metabolomics	Study of metabolic activity of the microbiome population
Prebiotic	Food ingredient that supports the growth of one or more members of the microbiota
Probiotic	Live organism that, when ingested, is believed to provide benefit to the host

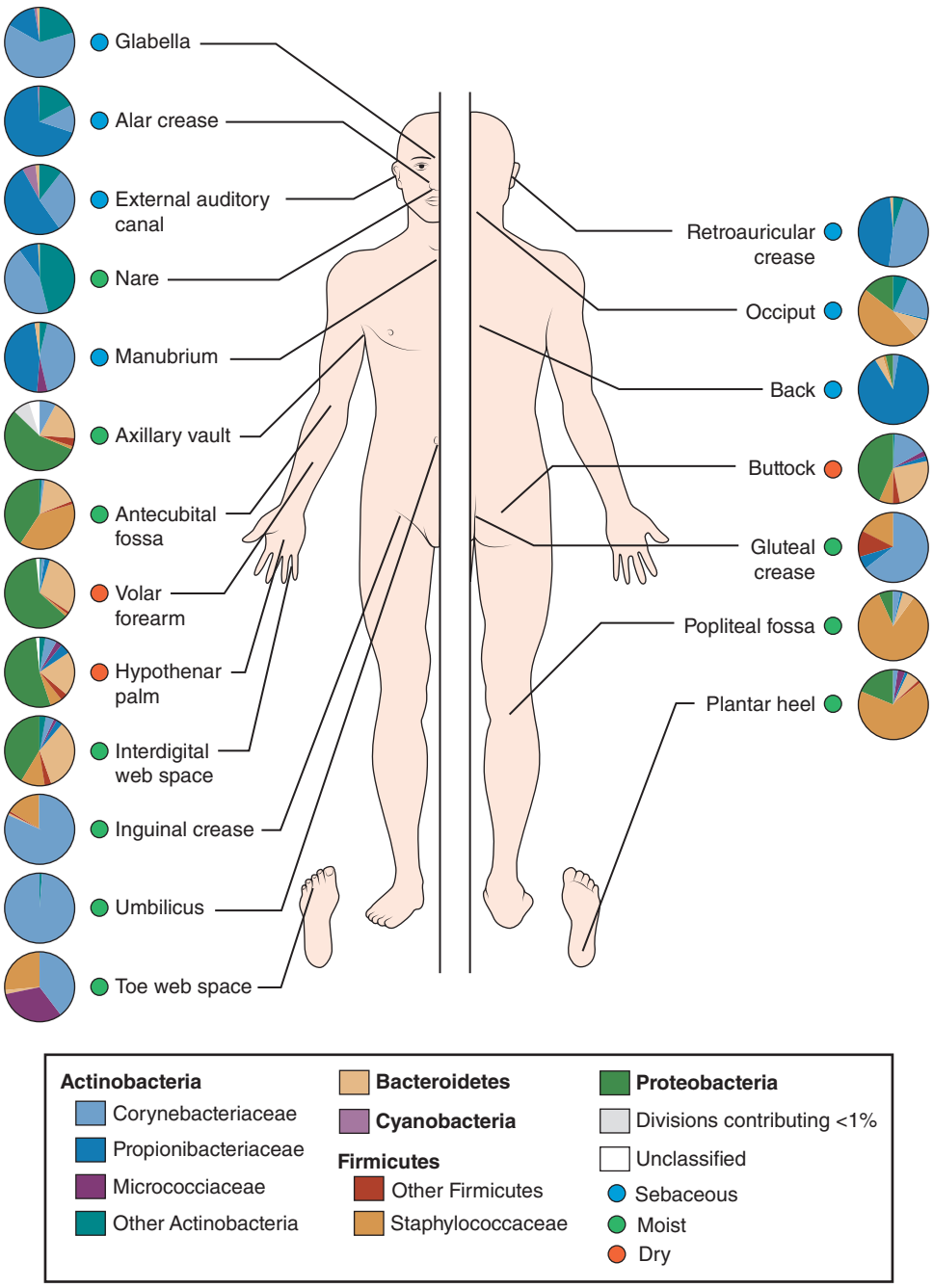

Fig. 2.1 Topographical distribution of bacteria on skin sites. As at other body sites, the distribution of the skin microbiome is dependent on the microenvironment of the sampled site, such as sebaceous or oily *(blue circles);* moist *(green circles);* and dry, flat surfaces *(red circles).* (From Grice, E., Segre, J., 2011. The skin microbiome. Nat. Rev. Microbiol. 9, 244–253.)

numerous, representing the majority of the total population, whereas the remaining portion of the population **(secondary microbiome)** consists of small numbers of many species that may not be widely shared by individuals. This would imply that the members of the core microbiome are critically important, providing essential functions that must be retained for normal metabolic and immunologic activities, and the functions provided by the secondary microbiome are also critically important but can be provided by a variety of organisms. In other words, although there is variation of species among individuals, there is less variation in the genetic composition at each site. The **taxonomic diversity** of a population is great, but the functional properties are highly conserved **(functional redundancy)** in microbiomes associated with health. This is not surprising if we consider that the microbiome is a community that exists in a symbiotic relationship with its host, providing needed metabolic functions, stimulating innate immunity, and preventing colonization with unwanted pathogens. Thus interpersonal variations of the microbiome can exist in healthy individuals as long as the needed functions are satisfied.

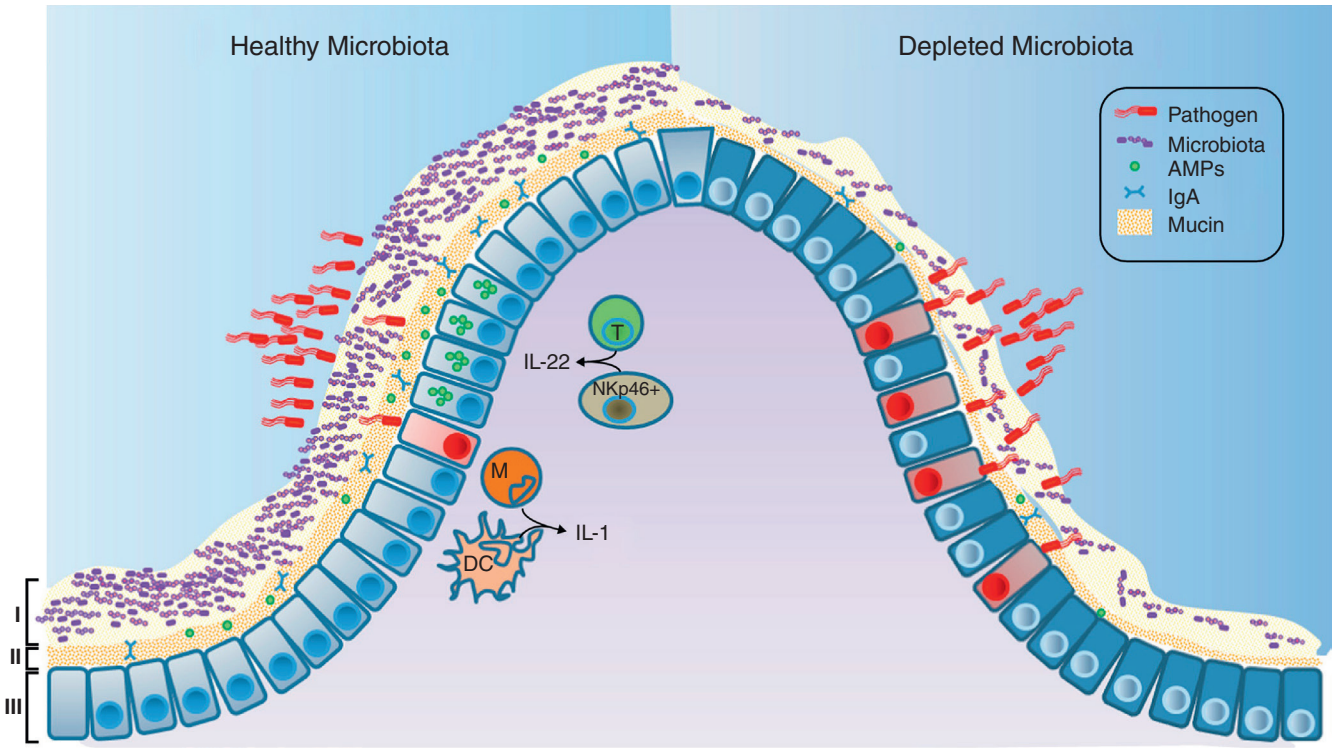

Fig. 2.2 Intestinal microbiota protection against enteric infections. (I) Saturation of colonization sites and consumption of nutrients limit pathogen access to host tissues; (II) the microbiota prime innate immunity by stimulating mucin production, immunoglobulin *(Ig)*A, and antimicrobial peptides *(AMPs);* and (III) the microbiota stimulate interleukin *(IL)*-22 expression, which increases epithelial resistance, and IL-1β production, which promotes recruitment of inflammatory cells. (From Khosravi, A., Mazmanian, S., 2013. Disruption of the gut microbiome as a risk factor for microbial infections. Curr. Opin. Microbiol. 16, 221–227.)

Evolution of the Microbiome and Normal Flora

The **normal flora** or microbial population of a particular site of the body consists of a unique community of core and secondary microbiota that evolved through a symbiotic relationship with the host and a competitive relationship with other species. The host provides a place to colonize, nutrients, and some protection from unwanted species (innate immune responses). The microbes provide needed metabolic functions, stimulate innate and regulatory immunity, and prevent colonization with unwanted pathogens (Fig. 2.2). The ability to tolerate the amount of oxygen or lack thereof (redox state) and the pH and salt concentration, as well as to scavenge essential minerals and harvest and metabolize the available nutrients, determines the numbers and nature of the species that populate a site of the body. Anaerobic or facultative anaerobic bacteria colonize most of the sites of the body because of the lack of oxygen in sites such as the mouth, intestine, and genitourinary tract.

The composition of the microbiota is influenced by personal hygiene (e.g., use of soap, deodorants, mouthwash, skin peels, enemas, vaginal douches), diet, water source, medicines (especially antibiotics), and exposure to environmental toxins. Drinking well water versus chlorinated city water or a diet consisting of fiber, sugar, or fats can select for different intestinal bacteria based on their ability to use the essential minerals (e.g., iron) and nutrients. Alteration of the environment with foods or medicines can also alter the microbiota (Fig. 2.3). These changes can be acceptable if the core microbiome and critical functional properties of the microbiome are maintained but can result in disease if these functions are lost. Historically, the greatest concern with the use of broad-spectrum antibiotics was the selection of resistant bacteria; however, a greater concern should be the disruption of the microbiome and loss of essential functions. Because antibiotics are not completely selective for the targeted pathogen, the use of antibiotics is always associated with some degree of toxicity.

Of the more than 150 species of bacteria that colonize the gut of a healthy adult individual, most are members of Bacteroidetes (e.g., *Bacteroides*) and Firmicutes (e.g., *Clostridium, Ruminococcus, Faecalibacterium, Lactobacillus*), with Actinobacteria (e.g., *Bifidobacterium*) present in smaller numbers. Interestingly, the importance of many of these bacteria was not appreciated before gene sequencing was used to identify and quantitate the gut microbiota. Within the colon, some bacteria establish their niche by waging interspecies warfare with bacteriocins (e.g., colicins produced by *Escherichia coli*), other antibacterial proteins, and metabolites that deter other species from growing. These molecules also benefit the host by eliminating invading bacteria including *Salmonella, Shigella, Clostridioides difficile, Bacillus cereus*, and other pathogens. The bacteria must also resist antimicrobial peptides and immunoglobulin (Ig) A produced by the host and released into the bowel.

Metabolism of nutrients plays a major role in the symbiotic relationship between the human host and microbe.

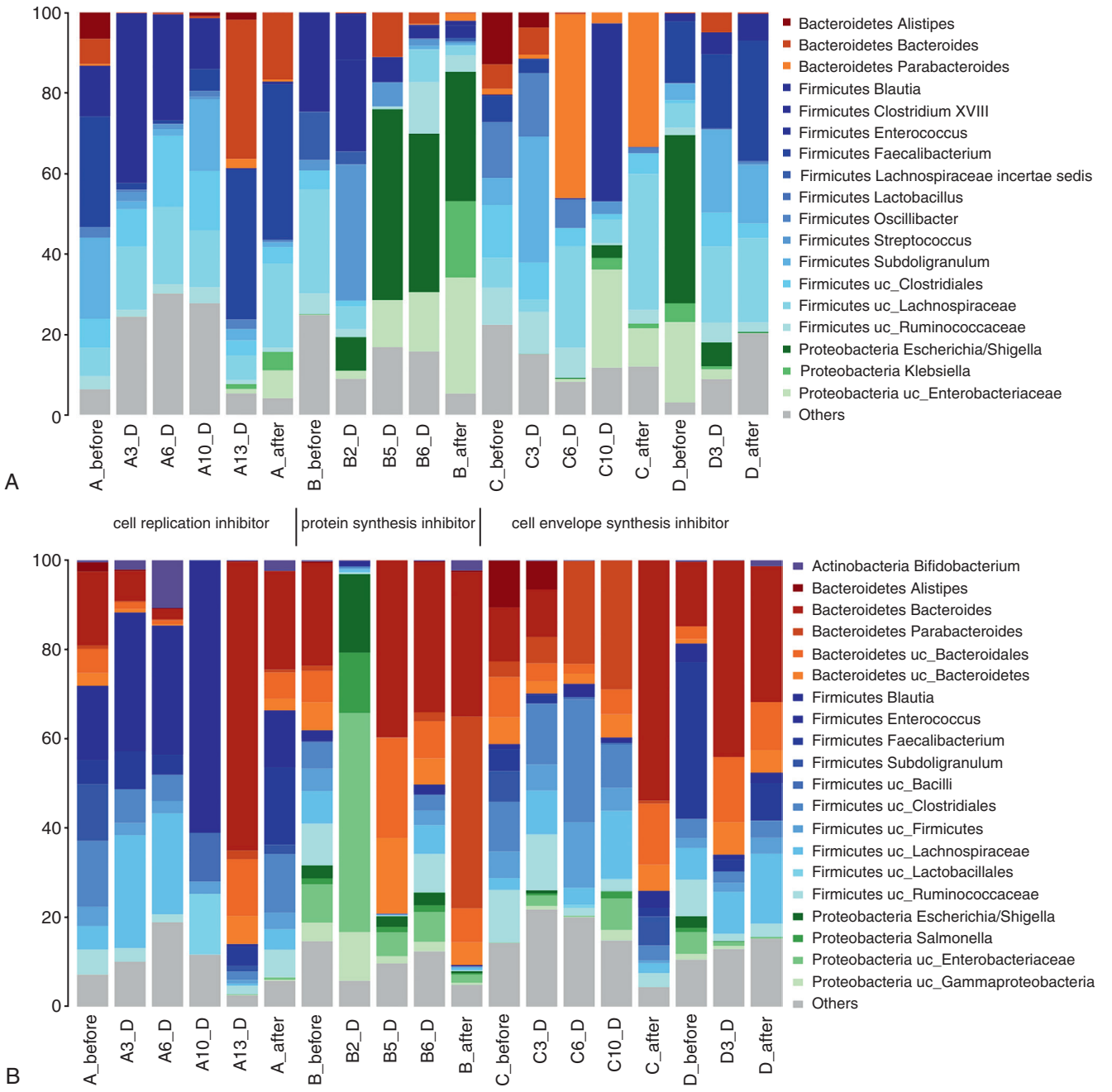

Fig. 2.3 Effect of antibiotics on the gut microbiota. Fecal samples were collected from four patients treated with antibiotics: patient A, moxifloxacin; patient B, penicillin + clindamycin; patient C, cefazolin followed by ampicillin/sulbactam; and patient D, amoxicillin. Fecal samples collected before, during (e.g., 3_D is day 3 of therapy), and after therapy were used to assess the total microbiota. Changes are noted both during therapy and after therapy is discontinued. (A) Total microbiota (16 S rRNA gene). (B) Metabolically active microbiota (16 S rRNA transcripts). (From Perez-Cobas, A.E., Artacho, A., Knecht, H., et al., 2013. Differential effects of antibiotic therapy on the structure and function of human gut microbiota. PLoS One 8, e80201.)

Bacteria in the human gut are responsible for metabolizing complex carbohydrates (including cellulose) to provide small-chain fatty acids such as acetate, propionate, and butyrate that can be readily transported and used by the cells of our body. These acids also limit the growth of undesirable bacteria. Other bacteria graze on the carbohydrates, the mucins that line the epithelium, or the oils released in our sweat. Bacteroidetes and Firmicutes are more efficient than others at breaking down complex carbohydrates, including plant cell wall compounds (cellulose, pectin, and xylan) and host-derived carbohydrates, including those attached to the mucins or chondroitin sulfates of the protective mucous layer of the intestine. Increases in the ratio of these bacteria in the gut microbiome can lead to a higher efficiency in the storage of the metabolic by-products. This can be a benefit for malnourished populations or patients with debilitating diseases such as cancer or can lead to obesity in well-nourished populations.

Role of the Microbiome in Disease

If the normal microbiome characterizes health, then alterations in the microbiome can signify disease; this is a relationship we are only beginning to understand. In 1884 Robert Koch and Friedrich Loeffler defined the relationship between an organism and infection. The **Koch postulates** were based on the concept of one organism: one disease. Microbiome research has introduced a new concept of disease caused by a community of organisms rather than a single species of bacteria, and the influence extends beyond traditional "infectious" diseases to include immunologic and metabolic disorders such as inflammatory bowel disease, obesity, type 2 diabetes, and celiac disease. We are now at the forefront of a new era of redefining the concept of health and disease.

Disruption of the normal microflora (commonly referred to as **dysbiosis**) can lead to disease by eliminating needed organisms or allowing the growth of inappropriate bacteria. For example, following exposure to antibiotics and suppression of the intestinal normal flora, *C. difficile* proliferates and expresses enterotoxins, leading to inflammation of the colon **(antibiotic-associated colitis)**. Another disease of the colon, **ulcerative colitis**, is associated with an increased level of bacteria-producing mucin-degrading sulfatases, leading to degradation of the protective mucosal lining of the intestinal wall and stimulation of inflammatory immune responses. Individuals with an intestinal microbiota that is more efficient at breaking down complex carbohydrates internalize rather than void these nutrients; therefore, they are susceptible to **obesity** and a predisposition to metabolic syndromes such as **type 2 diabetes**. Not all patients genetically predisposed to **celiac disease**, an immune-mediated enteropathy precipitated by exposure to gluten proteins, are symptomatic. The intestinal microbiota of most individuals is composed of bacteria capable of digesting glutens, which may be sufficient to protect these genetically predisposed individuals. In the absence of these bacteria, disease may occur. Shifts in the skin microbiome are associated with progression to **chronic wound infections** and episodic exacerbations of **atopic dermatitis**. Alteration in the vaginal microbiome from relatively few predominant, acid-tolerant organisms (e.g., *Lactobacillus*) to a heterogeneous mixed population of predominantly anaerobic bacteria is associated with the progression to **vaginitis**.

Diagnostics and Therapeutics

An understanding of the influence of dysbiosis on disease pathology can lead to both advanced diagnostic tests and paths for therapeutic intervention. Just as the presence of *Salmonella* or *Shigella* signifies disease, changes in the diversity and composition of the fecal microflora can also indicate susceptibility to or onset of disease. The most obvious example is *C. difficile* disease, a clinical disease preceded by a depletion of the normal flora because of antibiotic use. Interestingly, patients with chronic relapsing *C. difficile* infections are treated successfully by repopulating (some say **"repoopulating"**) the intestines with stool transplants from a healthy spouse or close relative or with artificially created stool specimens consisting of a complex mixture of aerobic and anaerobic fecal organisms.

More subtle alterations in the gut microbiome may predict the development of diseases such as **necrotizing enterocolitis (NEC)**, inflammatory bowel disease, and a predilection for obesity. NEC is a devastating intestinal disease that afflicts preterm infants. Prospectively collected stool samples from infants younger than 29 weeks' gestational age who develop NEC demonstrate a distinct dysbiosis prior to the development of the disease. Infants with early-onset disease have a dominance of Firmicutes (predominantly *Staphylococcus*), whereas infants with late-onset NEC have a dominance of Enterobacterales.

The effects of microbiome alterations have also been described for the pathogenesis of inflammatory bowel disease and colorectal cancer. The proliferation of bacteria such as *Akkermansia muciniphila* that produce mucin-degrading sulfatases is responsible for the degradation of the intestinal wall lining. Additionally, an increase in members of the anaerobic family Prevotellaceae leads to upregulation of chemokine-mediated inflammation. Enterotoxigenic *Bacteroides fragilis* can also induce T helper cell–mediated inflammatory responses that are associated with colitis and are a precursor to colonic hyperplasia and colorectal tumors. Finally, *Methanobrevibacter smithii*, a minor member of the gut microbiome, enhances the digestion of dietary glycans by *Bacteroides thetaiotaomicron* and other core intestinal bacteria, leading to the accumulation of fat.

Alterations of the microbiome leading to disease may not be characterized by the presence or absence of a specific microbe because more than one organism may provide the needed function. It is likely that future diagnostics will measure for the presence or absence of a specific gene product **(proteomics)** or metabolic function **(metabolomics)**.

Probiotics

Probiotics are mixtures of bacteria or yeast that when ingested colonize and proliferate, even temporarily, in the intestine. Consumers of probiotics believe they act by rebalancing the microbiome and its functions, such as enhancing the digestion of food and modulating the individual's innate and adaptive immune response. The most common reason people use over-the-counter probiotics is to promote and maintain regular bowel function and improve tolerance to lactose. Probiotics are commonly Gram-positive bacteria (e.g., *Bifidobacterium, Lactobacillus*) and yeasts (e.g., *Saccharomyces*). Many of these microbes are found in ingestible capsules and as food supplements (e.g., yogurt, kefir). Probiotics have been used to treat *C. difficile*–associated diarrhea and inflammatory bowel disease, to provide protection from *Salmonella* and *Helicobacter pylori* disease, as therapy for pediatric atopic dermatitis and autoimmune diseases, and even for a reduction in dental caries, although the value of probiotics for many of these conditions is unproven. While it is clear that changes in the microbiome are associated with specific diseases, it is unclear what combinations of microbes are required to rebalance the microbiome and affect health. Although probiotics are generally safe dietary supplements, many probiotics are ineffective. The species, mixture of species, and dose and viability of the

probiotic organisms within a probiotic formulation influence its potency, efficacy, and therapeutic potential. What is clear is that much like the use of complex artificial mixtures of organisms to treat recurrent *C. difficile* disease, carefully designed "smart probiotics" will likely be an important adjunct to medical therapy in the future.

Perspective

In the near future, with faster and cheaper DNA sequencing procedures, analysis of a person's microbiome may become a routine diagnostic test for predicting and treating a wide range of diseases. However, a number of questions remain to be resolved: can we predict disease in an individual by monitoring changes in the microbiome? Which changes, taxonomic or genetic function, are most important? Can we prevent disease or treat disease by reestablishing a healthy microbiome? Can this be done by prescribing specific replacement microbes (e.g., fecal transplant) or with a universal mixture (probiotic)? Can the use of metabolic supplements **(prebiotics)** promote a healthy microbiota? Will the use of antibiotics be replaced by the use of "smart microbiome" therapies? Other questions include: what is the role of the host genome, environmental factors, and our hygienic practices in shaping the microbiome? What will be the informatic requirements for guiding diagnostics or therapeutics? Regardless of the answers to these and other questions, it is certain that we are witnessing a new era of microbiology that can radically change our approach to the prediction, diagnosis, and treatment of disease.

For questions, see https://ebooks.health.elsevier.com

Supplemental Reading

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Questions

1. What is the relationship between the human genome and microbiome genetic material?
2. Explain the concepts of taxonomic diversity and genetic diversity.
3. Explain the concept of the core microbiome.
4. Give three examples of alterations of the microbiome (dysbiosis) that are associated with specific diseases.

3 Infection Prevention and Control

In the wake of the COVID-19 pandemic the threat to human health posed by infectious diseases is well documented. Healthcare-associated infections (HAIs) account for considerable morbidity and mortality and in many instances thwart the advances that have been made in modern medicine. Likewise, infections outside of the acute care hospital setting (i.e., ambulatory clinics, long-term care facilities) pose a threat to individuals undergoing medical procedures, those with chronic illnesses, the elderly, and those with immunocompromising conditions. As demonstrated by the COVID-19 pandemic, infections initiated outside of the health care setting may pose a threat for transmission in hospital as well as among those in the community.

HAIs are defined as infections that patients acquire while being treated for other conditions or that health care workers (HCWs) acquire while performing their duties within a health care setting. Common HAI types include pneumonia, gastrointestinal infections (including infection due to *Clostridioides difficile*), and surgical site infections (SSI). Several additional HAIs of great importance include those associated with medical devices (e.g., catheter-associated urinary tract infections [CAUTI], ventilator-associated pneumonia [VAP], and central line-associated bloodstream infection [CLABSI]).

HAIs constitute one of the most common complications of health care delivery, estimated to occur in approximately 10% of all hospital admissions worldwide. As such, every health care institution should have an infection prevention program (IPP) charged with monitoring, preventing, and controlling the spread of infection across the spectrum of health care.

Infection Prevention Program

Infection prevention (IPP) and control (IC) programs were initiated more than 50 years ago to prevent and control HAIs, including those caused by multidrug-resistant organisms (MDROs; resistant to at least one agent in each of three different classes of antimicrobial agents). The IPP committee should be multidisciplinary and include representatives from nursing, infectious diseases (ID), critical care, surgery, central processing, environmental services, occupational health, and the clinical microbiology laboratory (CML). The mission of IPPs involves conducting surveillance for HAIs; implementing isolation of infected or at-risk patients; investigating and intervening in suspected nosocomial transmission; educating health care personnel, patients, and visitors regarding IP; reporting infections to public health authorities; participating in antimicrobial and diagnostic stewardship and working with occupational health specialists to anticipate and avert preventable exposures and infections and to manage those that may occur.

Prevention and control of HAIs starts with the use and enforcement of Standard Precautions (SP). SPs are the basic practices that apply to all patient care, regardless of the infectious state of the patient, and apply to all settings where care is delivered. SPs protect health care personnel and prevent health care personnel or the environment from transmitting infection to other patients. SP includes hand hygiene, use of personal protective equipment (PPE, e.g., gloves, gowns, masks, eyewear), respiratory hygiene/cough etiquette, and sharps safety (engineering and work practice controls).

Many epidemiologically important bacteria, including MDROs, many viruses, and fungi (*Candida auris* and other species of *Candida*), are spread directly from person to person via the hands of health care personnel, from contaminated surfaces in the hospital environment, or from contaminated patient care equipment. As such, hand hygiene and adequate disinfection of equipment and hospital surfaces are important means of preventing spread. In addition to hand hygiene and disinfection, contact precautions with the use of barriers such as gowns and gloves are useful to interrupt the transmission of MDROs and other pathogens. Barrier precautions do not thwart all the nosocomial routes of transmission; however, the implementation of universal gowning and gloving may be a useful measure in the event of an outbreak in the ICU. Control of device-related infections has now been addressed using "care bundles." Care bundles in infection prevention and safety are simple sets of evidence-based practices that, when implemented collectively, improve the reliability of their delivery and improve patient outcomes. Commonly employed bundles include those for prevention of CLABSI, CAUTI, VAP, and SSI. These evidence-based preventive measures have been shown to be effective in reducing rates of device-related HAIs, as long as they are implemented with sustained effort.

Surveillance

In the United States (US), national and state accrediting agencies require hospitals to perform surveillance for HAIs. Surveillance allows the IPP to monitor the frequency and types of HAIs, direct outbreak investigations, evaluate compliance with IP mandates, provide data for policy development, and monitor the effect of IP interventions on rates of HAIs. Most acute care institutions (e.g., hospitals, long-term acute care facilities) in the US perform prospective incident surveillance of endemic infections. Surveillance may be targeted and/or hospital wide. Although continuous hospital-wide surveillance provides the most comprehensive view of HAIs, it is very resource intense and is not sustainable for most institutions. Targeted surveillance may focus on specific patient-care areas (e.g., ICUs), infection sites (e.g., UTIs, SSIs),

infections with certain organisms (e.g., methicillin-resistant *Staphylococcus aureus* [MRSA], MDROs, *C. difficile, C. auris*), infections that follow surgery, and the patient-care processes associated with infectious outcomes. To maximize the use of IP personnel, many hospitals have directed surveillance efforts toward device-related HAIs occurring in patient-care areas with the highest HAI risks (e.g., CLABSIs or VAPs in ICUs).

Surveillance in hospitals may take two different forms: passive surveillance and active surveillance. Passive surveillance involves collection of existing clinical and microbiologic data to track rates of infection or colonization and to detect unusual infections or clusters that may merit further investigation. Review of CML data remains the most common method for case finding in HAI surveillance. Laboratory-based surveillance allows the IPP personnel to review large amounts of data in an efficient manner. These efforts may be enhanced using medical information systems that can link laboratory data with data from other sources, including pharmacy, radiology, and nursing notes among others. When using data from the CML it must be recognized that the sensitivity and specificity of laboratory-based surveillance depend upon the frequency with which clinicians obtain cultures and the quality of the specimens received for culture in the CML. In most instances, the use of cultures sent for diagnostic purposes is unlikely to identify patients who are colonized with MDROs and who may serve as reservoirs for MDRO transmission.

Active microbial surveillance employs testing (using culture or molecular methods) specifically to screen patients for colonization with epidemiologically significant organisms (e.g., MDROs, MRSA, vancomycin-resistant enterococci [VRE], *C. auris*). In the US, screening for colonization with MRSA has been mandated in several states (as well as the Veterans Affairs [VA] health care system). Although controversial, these efforts have resulted in a significant reduction in MRSA infections in the VA system. In contrast, much less is understood concerning how best to apply active surveillance to prevent the transmission of MDROs, including MDR *Acinetobacter* or carbapenem-resistant Gram-negative bacilli (CR-GNB). Active surveillance is quite complex and resource intensive (requires cultures to be obtained from several anatomic sites from each patient) and should be limited to new introduction of problematic pathogens (MDROs, *C. auris*), continued transmission of MDROs despite implementation of standard and enhanced IP practices, or outbreak settings.

Personal Protective Equipment

PPE refers to protective clothing, helmets, gloves, face shields, goggles, face masks, and/or respirators or other equipment designed to protect the wearer from injury or the spread of infection or illness. PPE is commonly used in health care settings such as hospitals, doctor's offices, and clinical labs. PPE for HCWs includes gloves, gowns, eye/face protection (e.g., goggles, face shield), and NIOSH-certified, disposable N95 filter facepiece respirators or better. All hospital staff, patients, and visitors should use PPE when there will be contact with blood or other bodily fluids as well as when exposed to airborne diseases such as COVID-19. When used properly, PPE acts as a barrier between infectious materials such as viral, fungal, and bacterial contaminants and your skin, mouth, nose, or eyes (mucous membranes). The barrier has the potential to block transmission of contaminants from blood, body fluids, or respiratory secretions. PPE may also protect patients who are at high risk for contracting infections through a surgical procedure or who have a medical condition, such as an immunodeficiency, from being exposed to substances or potentially infectious material brought in by visitors and HCWs. When used properly and with other infection control practices such as handwashing, using alcohol-based hand sanitizers, and covering coughs and sneezes, it minimizes the spread of infection from one person to another. Effective use of PPE includes properly removing and disposing of contaminated PPE to prevent exposing both the wearer and other people to infection.

Antimicrobial and Diagnostic Stewardship

Antimicrobial resistance (AMR) is a well-recognized public health threat. Infections caused by MDROs are associated with significant morbidity, mortality, and cost. The emergence of AMR is correlated with incorrect antimicrobial prescribing patterns and a lack of consistent diagnostic procedures to detect and identify the pathogens involved, whether viral, bacterial, or fungal. It is recognized that the prompt initiation of antimicrobial agents to treat infections reduces morbidity and saves lives; however, approximately 30% of all antimicrobials prescribed in US acute care hospitals are either unnecessary or suboptimal, practices which contribute to the growing AMR problem. In addition to promoting AMR, the misuse of antimicrobial agents exposes patients to adverse effects of these drugs and can impact the health of patients who are not even exposed to them through the spread of resistant organisms and *C. difficile*. Given these concerns, the implementation of antimicrobial stewardship programs (AMS) can help clinicians improve clinical outcomes and minimize harm by improving antibiotic prescribing. The major purpose of AMS is to optimize the use of antimicrobial agents to achieve the best outcomes while minimizing adverse events and limiting selection pressures that drive the emergence of resistance.

Stewardship of limited antimicrobial resources has been employed to promote the rational, efficacious, and cost-effective use of these agents and has been endorsed by several organizations, including the Infectious Diseases Society of America, the Society for Healthcare Epidemiology of America, the Society of Infectious Diseases Pharmacists, the Alliance for the Prudent Use of Antimicrobials, the CDC, and the World Health Organization. Presently, every hospital in the US must now have both an active IPP and an AMS program for accreditation by the Joint Commission as well as a condition of participation for the Centers for Medicare and Medicaid Services (CMS). As is the case for IPPs, the composition of the AMS team is multidisciplinary and optimally should include an infectious diseases (ID) clinician, a hospital epidemiologist, a clinical pharmacist with training in ID, a clinical microbiologist, an information system specialist, and an IP professional. Given the limited sensitivity of most diagnostic testing, antimicrobial therapy is often administered on an empirical basis. Empirical therapy requires information

regarding the likely pathogen and its susceptibility to antimicrobial agents. As such, empirical antimicrobial therapy is guided by the development and distribution of unit-specific and tailored antibiograms listing the most likely pathogens and their antimicrobial susceptibility profile. These antibiograms should be updated annually and provided to clinicians for use at the bedside. Such information may be used for clinician education as well as to evaluate important trends in AMR occurring by species of organism and/or hospital unit (e.g., ICU). Collaboration between the members of the AMS and with the IPP and the pharmacy and therapeutics (PT) committee is essential and must be supported by the administration and medical staff leadership.

The foundation for the AMS program depends on two complementary core strategies: prospective audit of antimicrobial usage with intervention and feedback and formulary restriction and preauthorization for selected antimicrobial agents. The conducting of prospective audits of antimicrobial use and any associated resistance issues is a daunting process if laborious chart reviews are required for each patient on antimicrobial therapy. Health care information technology and computer-based surveillance can improve antimicrobial decision-making by providing patient-specific microbiology results, targeting interventions, and tracking resistance patterns. The use of a computer decision support system can streamline the data review process by automatically alerting the AMS team when restricted drugs are ordered, showing patient location, identifying what other drugs the patient is receiving, and highlighting pertinent microbiology laboratory results. Additional considerations for streamlining antimicrobial management include notification if a patient was receiving double antimicrobial coverage or no antimicrobial coverage for an identified pathogen, identification of potential candidates for a switch from intravenous to oral therapy or for discontinuation of therapy when cultures fail to detect a potential pathogen.

Microbiological support is essential to direct patient-specific therapeutic interventions as well as assisting in infection control efforts. Implementation of newer immunological, molecular, and proteomic tests promises to enhance such efforts. Given the attraction of rapid molecular diagnostic tests to enhance the diagnosis and treatment of HAIs, attention has been turned to adding diagnostic stewardship (D×S) as a complement to existing IPP and AMS efforts. D×S is described as interventions prioritizing the right test, for the right patient, to prompt the right action. These actions not only improve test utilization and contribute to timely and appropriate diagnosis of HAI but also seek to improve antimicrobial use, to reduce antimicrobial resistance, and to enable better use of health care resources to improve patient outcomes. In most settings, D×S focuses on commonly used microbiology tests that are drivers of antimicrobial use such as blood cultures and cultures of respiratory tract and urine samples. In the present era of more costly, yet useful, molecular diagnostic tests, D×S should also be used to increase test use in settings with a high probability of disease and to decrease test use in low probability settings where the potential for false-positive results may result in patient harm. D×S should be embraced as a core activity to enable successful IP and AMS. The potential of each of these stewardship activities for infection management is enhanced by the integration of all three programs in a multidisciplinary fashion.

Sterilization, Disinfection, and Antisepsis

An important aspect of the control of infections is an understanding of the principles of sterilization, disinfection, and antisepsis (Box 3.1).

Sterilization

Sterilization is the destruction of all microbes, including the more resilient forms such as bacterial spores, mycobacteria, nonenveloped (nonlipid) viruses, and fungi. This can be accomplished using physical, gas vapor, or chemical sterilants (Table 3.1).

Saturated steam under pressure is a widely used, inexpensive, nontoxic, and reliable method of sterilization. Three parameters are critical: the time of exposure to steam, temperature, and amount of moisture. The most used sterilization cycle is use of saturated steam heated at 121°C for 15 minutes. Maintaining the proper temperature is critical because a drop of 1.7°C increases the needed exposure time by 48%. If no moisture is present, then the temperature must reach 160°C. Dry heat sterilization requires prolonged exposure times and damages many instruments, so it is not currently recommended.

Ethylene oxide gas is used to sterilize temperature- or pressure-sensitive items. Treatment is generally for 4 hours, and sterilized items must be aerated for an additional 12 hours to eliminate the toxic gas before the items are used. Although ethylene oxide is highly efficient, strict regulations limit its use because it is flammable, explosive, and carcinogenic to laboratory animals. For these reasons, ethylene oxide sterilization is avoided if acceptable alternatives are available.

Hydrogen peroxide vapors are effective sterilants because of the oxidizing nature of the gas. This sterilant is used for the sterilization of instruments. A variation is **plasma gas sterilization**, in which hydrogen peroxide is vaporized, and then reactive free radicals are produced with either microwave-frequency or radio-frequency energy.

Box 3.1 Definitions

Antisepsis: Use of chemical agents on skin or other living tissue to inhibit or eliminate microbes; no sporicidal action is implied

Disinfection: Use of physical procedures or chemical agents to destroy most microbial forms; bacterial spores and other relatively resistant organisms (e.g., mycobacteria, viruses, fungi) may remain viable; disinfectants are subdivided into high-, intermediate-, and low-level agents

Germicide: Chemical agent capable of killing microbes; includes virucide, bactericide, sporicide, tuberculocide, and fungicide

High-level disinfectant: A germicide that kills all microbial pathogens except large numbers of bacterial spores

Intermediate-level disinfectant: A germicide that kills all microbial pathogens except bacterial endospores

Low-level disinfectant: A germicide that kills most vegetative bacteria and lipid-enveloped and medium-size viruses

Sterilization: Use of physical procedures or chemical agents to destroy all microbial forms, including bacterial spores

Table 3.1 Methods of Sterilization

Method	Concentration or Level
PHYSICAL STERILANT	
Steam under pressure	121°C or 132°C for various time intervals
Filtration	0.22- to 0.45-µm pore size; HEPA filters
Ultraviolet radiation	Variable exposure to 254-nm wavelength
Ionizing radiation	Variable exposure to microwave or gamma radiation
GAS VAPOR STERILANT	
Ethylene oxide	450–1200 mg/L at 29°C–65°C for 2–5 h
Hydrogen peroxide vapor	30% at 55°C–60°C
Plasma gas	Highly ionized hydrogen peroxide gas
CHEMICAL STERILANT	
Peracetic acid	0.2%
Glutaraldehyde	2%

HEPA, High-efficiency particulate air.

Because this is an efficient sterilizing method that does not produce toxic by-products, plasma gas sterilization has replaced many of the applications for ethylene oxide. However, it cannot be used with materials that absorb hydrogen peroxide or react with it.

Two **chemical sterilants** have also been used: **peracetic acid** and **glutaraldehyde**. Peracetic acid, an oxidizing agent, has excellent activity, and its end products (i.e., acetic acid and oxygen) are nontoxic. In contrast, safety is a concern with glutaraldehyde, and care must be taken when handling this chemical.

Disinfection

Microbes are also destroyed by disinfection procedures, although more resilient organisms can survive. Unfortunately, the terms *disinfection* and *sterilization* are casually interchanged and can result in some confusion. This occurs because disinfection processes have been categorized as high, intermediate, and low level. High-level disinfection can generally approach sterilization in effectiveness, whereas spore forms can survive intermediate-level disinfection, and many microbes can remain viable when exposed to low-level disinfection. Even the classification of disinfectants (Table 3.2) by their level of activity is misleading. The effectiveness of these procedures is influenced by the nature of the item to be disinfected, number and resilience of the contaminating organisms, amount of organic material present (which can inactivate the disinfectant), type and concentration of disinfectant, and duration and temperature of exposure.

High-level disinfectants are used for items involved with invasive procedures that cannot withstand sterilization procedures (e.g., certain types of endoscopes and surgical instruments with plastic or other components that cannot be autoclaved). Disinfection of these and other items is most effective if cleaning the surface to remove organic matter precedes treatment. Examples of high-level disinfectants include treatment with moist heat and use of liquids such as glutaraldehyde, hydrogen peroxide, peracetic acid, and chlorine compounds.

Table 3.2 Methods of Disinfection

Method	Concentration (Level of Activity)
HEAT	
Moist heat	75°C–100°C for 30 min (high)
LIQUID	
Glutaraldehyde	2%–3.2% (high)
Hydrogen peroxide	3%–25% (high)
Chlorine compounds	100–1000 ppm of free chlorine (high)
Alcohol (ethyl, isopropyl)	70%–95% (intermediate)
Phenolic compounds	0.4%–5.0% (intermediate/low)
Iodophor compounds	30–50 ppm of free iodine per liter (intermediate)
Quaternary ammonium compounds	0.4%–1.6% (low)

ppm, Parts per million.

Table 3.3 Antiseptic Agents

Antiseptic Agent	Concentration
Alcohol (ethyl, isopropyl)	70%–90%
Iodophors	1–2 mg of free iodine per liter; 1%–2% available iodine
Chlorhexidine	0.5%–4.0%
Parachlorometaxylenol	0.50%–3.75%
Triclosan	0.3%–2.0%

Intermediate-level disinfectants (i.e., alcohols, iodophor compounds, phenolic compounds) are used to clean surfaces or instruments on which contamination with bacterial spores and other highly resilient organisms is unlikely. These have been referred to as semicritical instruments and devices and include flexible fiberoptic endoscopes, laryngoscopes, vaginal specula, anesthesia breathing circuits, and other items.

Low-level disinfectants (i.e., quaternary ammonium compounds) are used to treat noncritical instruments and devices, such as blood pressure cuffs, electrocardiogram electrodes, and stethoscopes. Although these items come into contact with patients, they do not penetrate through mucosal surfaces or into sterile tissues.

The level of disinfectants used for environmental surfaces is determined by the relative risk these surfaces pose as a reservoir for pathogenic organisms. For example, a higher level of disinfectant should be used to clean the surface of instruments contaminated with blood than that used to clean surfaces that are "dirty," such as floors, sinks, and countertops. The exception to this rule is if a particular surface has been implicated in a nosocomial infection, such as a bathroom contaminated with *C. difficile* (spore-forming anaerobic bacterium) or a sink contaminated with *Pseudomonas aeruginosa*. In these cases, a disinfectant with appropriate activity against the implicated pathogen should be selected.

Antisepsis

Antiseptic agents (Table 3.3) are used to reduce the number of microbes on skin surfaces. These compounds are selected for their safety and efficacy. A summary of their germicidal properties is presented in Table 3.4.

Table 3.4 Germicidal Properties of Disinfectants and Antiseptic Agents

Agents	Bacteria	Mycobacteria	Bacterial Spores	Fungi	Viruses
DISINFECTANTS					
Alcohol	+	+	–	+	+/–
Hydrogen peroxide	+	+	+/–	+	+
Phenolics	+	+	–	+	+/–
Chlorine	+	+	+/–	+	+
Iodophors	+	+/–	–	+	+
Glutaraldehyde	+	+	+	+	+
Quaternary ammonium compounds	+/–	–	–	+/–	+/–
ANTISEPTIC AGENTS					
Alcohol	+	+	–	+	+
Iodophors	+	+	–	+	+
Chlorhexidine	+	+	–	+	+
Parachlorometaxylenol	+/–	+/–	–	+	+/–
Triclosan	+	+/–	–	+/–	+

Alcohols have excellent activity against all groups of organisms except spores and are nontoxic, although they tend to dry the skin surface because they remove lipids. They also do not have residual activity and are inactivated by organic matter. Thus the surface of the skin should be cleaned before alcohol is applied.

Iodophors are also excellent skin antiseptic agents, having a range of activity similar to that of alcohols. They are slightly more toxic to the skin than alcohol, have limited residual activity, and are inactivated by organic matter. Iodophors and iodine preparations are frequently used with alcohols for disinfecting the skin surface.

Chlorhexidine has broad antimicrobial activity, although it kills organisms at a much slower rate than alcohol. Its activity persists, although organic material and high pH levels decrease its effectiveness. The activity of **parachlorometaxylenol** is limited primarily to Gram-positive bacteria. Because it is nontoxic and has residual activity, it has been used in handwashing products.

Triclosan is active against bacteria but not against many other organisms. It is a common antiseptic agent in deodorant soaps and some toothpaste products.

Role of the Clinical Microbiology Laboratory in Support of Infection Prevention

To prevent the occurrence of HAIs, one must first be able to detect them when they occur. As such, the CML plays a key role in HAI prevention. Some of the major roles played by the CML in IP include contributions to (1) surveillance, (2) detection and characterization of emerging pathogens and AMR, (3) outbreak detection and management, (4) antimicrobial and diagnostic stewardship, (5) performance of supplementary cultures, (6) molecular typing of epidemiologically important organisms, (7) development of an organism bank, and (8) education.

Surveillance

As noted previously under the discussion of the IPP, review of data from the CML remains the most common method for case finding in HAI surveillance. Thus the CML must promptly and accurately detect nosocomial pathogens and characterize their resistance patterns. Such data must be not only generated in a timely fashion but must be rapidly transmitted to the clinical team, the IPP, and applicable public health authorities. Given that the results of routine cultures submitted to the CML for the diagnosis of HAI constitute the primary means of HAI surveillance, the laboratory often serves as an "early warning system" by identifying clusters of organisms with unique phenotypic characteristics and promptly communicating results to the IPP. The accuracy and precision of the systems used in the CML for identification of organisms have important implications for HAI prevention efforts. Laboratories that have the means to identify HAI pathogens the species level may detect outbreaks that would otherwise have gone undetected with less specific identification efforts (e.g., reporting "*Klebsiella*/*Enterobacter*" or "*Klebsiella* species" rather than *Klebsiella oxytoca*). Incomplete or incorrect identification of organisms may obscure problem areas. Conversely, advances in organism identification with methods such as matrix-assisted laser desorption ionization-time-of-flight mass spectrometry (MALDI TOF MS) or DNA sequencing may lead laboratories to identify the species-level organisms that were previously lumped into large categories (e.g., diphtheroids) signifying probable contaminants. Whereas most clinicians are familiar with the label "diphtheroids" and generally consider them to be either contaminants or less clinically important microbes, the report of specific organisms (e.g., *Brevibacterium casei*) may be confusing and lend more importance to the result than the generic term "diphtheroids" would warrant, leading to inappropriate antimicrobial therapy.

The success of any program to control MDROs depends on the ability of the CML to detect these organisms. Laboratory

directors should be aware that various organizations, including the Clinical and Laboratory Standards Institute, the European Committee on Antimicrobial Susceptibility Testing (EUCAST), and the CDC, publish and regularly update guidance on best practices for MDRO testing. If the CML uses methods that do not accurately identify organisms or specific resistance patterns, the IPP may not identify serious problems or outbreaks. Conversely, IP personnel may investigate spurious problems, thereby diverting and wasting precious resources.

Emerging Pathogens and Antimicrobial Resistance

Gram-positive cocci (GPC), largely staphylococci and enterococci, played a dominant role in HAIs during the 1990s and early 2000s. Indeed, AMR was personified by MRSA and VRE. These two antimicrobial-resistant pathogens were deemed the "most out of control" HAI pathogens in US hospitals in 2003. Subsequently, infections with GNB have overtaken those due to GPC and *Candida* species have become the most frequent cause of CLABSI in adult ICUs. The widespread use of multiple classes of antibacterial and antifungal agents within the ICU setting makes critical care areas the epicenter for the acquisition and dissemination of resistance in bacteria and fungi alike. The introduction and spread of *C. auris*, an emerging opportunistic fungal pathogen, is an example of the importance of CML in detecting and characterizing MDRO pathogens. Following the initial detection of *C. auris* in 2009, this species has spread worldwide causing serious infection and death in hospitalized patients in over 30 countries and 6 continents. *C. auris* is characterized by the ability to survive on inanimate surfaces, prolonged colonization of infected and uninfected patients, transmission from patient to patient in the health care environment, and a propensity to express resistance to multiple classes (azoles, echinocandins, and polyenes) of antifungal agents. Notably, *C. auris* is not identified by most commercial systems employed in routine CMLs and requires the use of either MALDI TOF MS or DNA sequencing for a definitive identification. Given its MDR profile and ability to survive in the hospital environment with documented spread from patient to patient, the CDC now considers *C. auris* a serious global threat.

The species of GNB that are the most important when considering MDROs as causes of HAI include several members of the *Enterobacterales* including *Klebsiella* and *Enterobacter* spp. as well as the nonfermentative GNBs *Acinetobacter baumannii* and *Pseudomonas aeruginosa*. These organisms express several different β-lactamases that may pose some difficulty to detect using routine phenotypic microbiological methods. Thus the CML must detect and characterize not only MRSA and VRE but also resistance to β-lactams and carbapenems in *Enterobacterales*, MDR in *Acinetobacter* and *Pseudomonas* spp., and azole and echinocandin resistance in *Candida* spp. The CMLs' role in monitoring resistance is extremely important to the success of the IP effort. CML personnel must notify IPP staff promptly when key resistant pathogens are detected and when new resistant phenotypes are identified so that appropriate IC precautions are applied.

The introduction and spread of respiratory viruses (e.g., respiratory syncytial virus [RSV], influenza, parainfluenza among others) is always a concern for IP in hospital. In most instances, infected individuals are kept out of the hospital, and when admission is required, the infected patient is placed under negative pressure isolation and attended to by HCW using appropriate PPE. The worldwide coronavirus disease 2019 (COVID-19) pandemic has posed a tremendous challenge to patients, communities, hospitals and governments. During this pandemic, the IPP and CML have been on the frontline in the effort to diagnose symptomatic patients so they can be considered for antiviral therapy and adjunctive treatments, place infected patients in the most appropriate setting (single room or cohorted in a room or ward with other infected patients), screen asymptomatic patients preadmission to ensure correct placement to minimize patient-to-patient transmission, ensure that HCWs coming into direct contact with patients with COVID-19 use appropriate PPE, and test symptomatic HCWs to ensure appropriate isolation of those who test positive to minimize HCW-to-patient transmission. The IPP and hospital's ability to meet these ends depends directly on the CMLs' ability to meet an overwhelming demand for testing. As the pandemic progressed, CML personnel have been involved in many other efforts beyond testing and reporting: test development, dealing with supply chain issues, and serving as advisors to IPPs, health care providers, and hospital leaders regarding a wide range of testing issues.

Outbreak Detection and Management

Most HAIs are not associated with outbreaks or epidemic infections; however, when confronted with a cluster or outbreak of HAIs, the IPP personnel must act quickly to characterize and define the scope of the outbreak, to identify possible causes, and to design and implement effective control measures. The CML must strive for early recognition of possible clusters and outbreaks, rapid notification and collaboration with the IPP staff, perform additional case finding, and provision of molecular typing for determination of relatedness, which requires maintenance of an organism bank. During an outbreak, the CML must partner with IP personnel to (1) provide information on the epidemiology of the infectious agent; (2) identify and store the isolates involved for further characterization; (3) design/select appropriate selective isolation media and drug susceptibility testing; and (4) perform supplemental microbiological surveillance of patients, personnel or environmental sources of infection. The CML and IPP should jointly consider the implementation of real-time data mining programs that can facilitate early detection of clusters by raising flags based on subtle changes in the rates of test ordering or of positive test results.

One issue of concern that directly involves the CML is that of a pseudo-outbreak. A pseudo-outbreak occurs when an apparent outbreak turns out not to be an outbreak at all. The usual cause of a pseudo-outbreak is either misdiagnosis (e.g., infection has not occurred) or misinterpretation of epidemiological data (e.g., infections have occurred, but clustering or epidemic transmission has not). The CML may

also be the source of a pseudo-outbreak via contamination of stains or reagents, false antimicrobial susceptibility results, or false-positive rapid diagnostic test results.

Supplemental Cultures

The CML is frequently called upon to detect potential HAI pathogens that may be colonizers of patients, HCWs, or the health care environment. Such cultures may require the use of selective, enrichment, or differential media that enhance the ability of CML staff to identify the reservoir and the pathogens of interest. Patients and HCWs are increasingly screened for carriage of pathogens of epidemiological importance such as MRSA, VRE or, MDR-GNBs, often as one aspect of an enhanced program for MDRO control. Screening for other organisms (e.g., Group A streptococci, *C. auris*) may be performed as part of an HAI outbreak investigation. Finally, hand cultures of HCWs may be performed as part of educational efforts in support of a hand hygiene campaign or to confirm the mechanism of cross-infection during an outbreak investigation.

At one time, the hospital environment was considered to be a major source of HAI pathogens. Subsequently, it has been recognized that patients often acquire infection from their own colonizing (endogenous) flora. Although there are specific circumstances in which environmental sampling (e.g., surfaces, water, air, medication) for quality assurance (QA) or for detection of potential pathogens is required, sampling of inanimate objects or surfaces is warranted only when a careful epidemiological investigation suggests that a specific material or surface may be implicated in pathogen transmission. Routine undirected cultures of samples from HCWs or the environment should be discouraged. Both IPP and CML staff members should understand that such cultures are labor intensive and nonstandardized and rarely provide useful information. Such sampling should only be performed as part of an epidemiological investigation in consultation with a health care epidemiologist. When such an investigation reveals a common organism in patient, HCW, and/or environmental samples, the CML should also provide access to molecular strain typing methods.

Molecular Strain Typing in Support of IP Activities

The laboratory characterization of HAI pathogens to provide evidence for their genetic and biologic relatedness is often useful to epidemiologists as an aid in investigating HAIs. There are several situations where it is important to determine if two or more organisms are genetically related and thus likely to have a common source: (1) outbreaks, clusters, and other transmission events where evidence for patient-to-patient transmission or a common reservoir of infection is sought; (2) determination of the origin of an individual infection (e.g., comparison of an infecting isolate to those previously found as colonizers or in the environment); (3) surveillance for emergence or spread of a particularly virulent or epidemic clone (e.g., the BI/NAP1 strain of *C. difficile*, *C. auris*).

Molecular strain typing employs a range of techniques ranging from simple plasmid profiling to whole genome sequencing (WGS). Strain typing is performed to determine whether various isolates yield the same or different profile using one or more molecular tests. If isolates from different patients show the same result or "fingerprint", the isolates likely originated from a single clone and were transmitted from patient to patient (or HCW to patient) from a common source or by a common mechanism. Increasingly, the use of traditional typing methods such as pulsed-field gel electrophoresis, has been found to lack sufficient power to allow fine epidemiological discrimination of closely related bacterial or fungal isolates. As such, WGS has been shown to provide high resolution genetic analysis sufficient to delineate epidemiologically related from unrelated strains. Recent improvements in sequencing technologies and data analysis tools have improved the applicability of WGS for use in the health care environment.

Genotypic typing methods provide meaningful data and are cost-effective only when they are used for well-defined epidemiological objectives. In addition to the situations mentioned above, these objectives include (1) determining the source and extent of an outbreak; (2) determining the mode of transmission of an HAI pathogen; (3) evaluating the efficacy of preventative measures; (4) monitoring transmission in high-risk areas such as ICUs where cross-infection is likely.

Organism Banking and Storage

It is impossible for the CML to perform supplemental testing, such as molecular typing or further characterization of resistance, if the appropriate isolates have not been saved. As such, one of the CMLs critical responsibilities is to save all potentially relevant organisms in case further analysis is needed. An organism bank provides for long-term viability and availability of significant bacterial and fungal isolates for both clinical and epidemiological use. The major purposes of an organism bank are (1) for patient care use in retrieval of earlier isolates if the patient remains infected, (2) epidemiological investigation of clusters of organisms, and (3) research purposes and having access to a wide range of clinical isolates for new method evaluation. In the interest of patient care, as well as for IP purposes, the CML should plan and routinely save all epidemiologically important isolates from routine diagnostic cultures. Designation of isolates to be saved and for how long should be determined jointly by CML and IPP personnel. It has been recommended that all isolates from normally sterile sites (e.g., blood, cerebrospinal fluid, joint fluid), important MDROs (e.g., MRSA, VRE, CR-GNB, and ESBL-producing GNBs) from any site, and other epidemiologically important pathogens (e.g., *M. tuberculosis*, *Legionella*, *C. auris*) be saved for a period of three to five years. Culture collections in an organism bank that are linked to patient demographics and organism characteristics are essential in epidemiologic outbreak investigations. Important data elements should be stored in the electronic medical record, laboratory information system or a separate database. Access and integration of these data in relation to the organisms are important for investigations. Advances in computer decision support

can allow analysis of data elements from several information systems, allowing real-time surveillance for outbreak detection.

Education

CML personnel play a major role in the education of clinicians, future hospital epidemiologists, infectious diseases specialists, and IP personnel in basic microbiological principles and practices. Whereas most hospital epidemiologists are trained in infectious diseases, most IPP personnel have not worked in, or have been exposed to, CMLs and would benefit from such educational efforts. To maximize the efficacy of IPPs, the CML should provide training and education on basic microbiology and biosafety for HCWs in areas such as specimen procurement, handling, and transport; epidemiologically important pathogens versus normal flora; and interpretation of microbiological results. Both the CML and IPP can benefit if the IPP staff understands the routine processes of the laboratory, such as the daily workflow employed for processing specimens such as blood, urine, or wound cultures and related procedures. The CML should educate clinicians about the introduction of new tests or order sets and how specific tests should be used in clinical situations as well as how to interpret test reports. This information allows the IPP and clinical personnel to set expectations regarding turnaround times for specific results and time constraints of the CML test services. Written/electronic guidelines regarding sample collection, handling, and transport should be available in every ward, which can also include details on the tests available for isolation, identification, and typing of HAI pathogens.

There are several ongoing trends that complicate the valuable personal interactions between the CML, the IPP, and clinicians. Consolidation of CML services, off-site moves of CMLs (often to a commercial laboratory), and total reliance on the electronic medical record to the exclusion of firsthand observation (e.g., review of culture plates or stains) too often limits the access of clinicians and IPP personnel to the laboratory and keeps microbiologists confined to the laboratory.

Infection Prevention and Control in the Community

The past three decades have been characterized by a steady shift from the hospital to the outpatient setting in most areas of health care. The increase in the number of patients undergoing ever more complicated forms of medical therapy in the ambulatory setting, exposes an increasingly vulnerable patient population to considerably greater risks of iatrogenic infection. The shift in the provision of medical care from inpatient to outpatient health care services has posed a tremendous challenge for institutional IPPs. The rates of community healthcare-associated infections (cHAI) are comparable to rates found in the acute hospital setting (5%–12%), but the types of infection differ with a greater focus on UTIs in the community and VAP in the hospital setting. The basic practices of IP/IC in the inpatient setting also need to be applied to the outpatient settings, including the need to collect data on infection rates, develop formal policies and procedures and intervene directly to prevent infections.

Ambulatory outpatient care is now offered in a variety of settings including infusion therapy, dialysis, and endoscopy. In addition, many surgical procedures performed previously only on inpatients are now routinely performed in ambulatory surgical settings. Additional risks may be related to patient placement, environmental disinfection, equipment reuse, or cleaning/sterilization, communicable disease transmission, and the type of procedure performed. cHAIs are defined as those occurring in individuals that have received specific home care (e.g., wound care, maintenance of vascular devices) or attended a hospital clinic in the 30 days prior to the infection, were hospitalized for 2 or more days in the 90 days prior to the infection or resided in a nursing home or long-term care facility.

IP/IC in the community can involve (1) attention to hand hygiene, (2) maintaining a clean living/patient care area, (3) close attention to vaccination status and administration of medications, and (4) nonpharmaceutical interventions such as community mitigation strategies. Importantly the IPP must implement work practices that prevent the transmission of infectious agents using a two-tiered approach: Standard Precautions and Transmission-Based Precautions.

Standard Precautions

All health care settings must make IP a priority and must be equipped to observe Standard Precautions (SPs). SPs are the minimum IP practices that apply to all patient care, regardless of infection status of the patient, in any setting where health care is provided. SPs include hand hygiene; use of PPE (e.g., gowns, gloves, masks); safe injection practices; safe handling of potentially contaminated equipment or surfaces in the patient environment; respiratory hygiene/cough etiquette.

Hand hygiene must be employed in several key patient care situations including before contact with a patient, before performing an aseptic task, after contact with a patient or objects, after contact with blood or body fluids, after removal of PPE, and when moving from dirty to clean site during patient care. Whereas an alcohol-based hand rub is preferred for most situations where hand hygiene is required, it should be noted that soap and water must be used initially when there is visible soiling or following care of patients with *C. difficile* infection (CDI) or norovirus infection.

PPE includes gloves, gowns, face masks, respirators, goggles, and face shields among others. PPE must be readily available with a proper selection for the anticipated use. Hand hygiene must be performed following removal of all PPE.

Injection safety is important to prevent transmission between patients or between patients and HCW during the preparation and administration of parenteral medications. Safe injection practices are necessary to avoid the use of a single syringe to administer medications to multiple patients, avoid the reuse of a syringe to enter a medication

vial, prevent the administration of medications from a single-dose or single-use vials to more than one patient, fluid administration sets and multidose vials must be dedicated to a single patient, safe disposal of all sharps, and use of face masks when placing catheters or injecting medications into the epidural or subdural space.

Environmental cleaning should provide for prompt and appropriate cleaning of all spills. Only Environmental Protection Agency disinfectants or detergents registered for use in health care should be used and applied according to manufacturer's directions for use.

Medical devices for reuse (e.g., endoscopes, bronchoscopes, endotracheal tubes) must be cleaned and maintained according to manufacturer's instructions to prevent patient-to-patient transmission of infectious agents.

Respiratory hygiene should target patients and accompanying family and friends with potentially transmissible respiratory infections. IP measures should be implemented at the first point of contact with the health care facility. IP measures include hand hygiene, provision and disposal of tissues, masking of coughing or otherwise symptomatic individuals, physical distancing with use of a separate area while waiting for care.

Transmission-Based Precautions

The variety of bacterial and viral pathogens that cause respiratory tract infections (RTI) in the ambulatory care setting creates a unique set of challenges for prevention and control. In addition to SPs, it is advisable to address airborne or highly communicable infections based on the mode of transmission and adaptation of CDC guidelines for isolation. Even before a pathogen has been detected, ambulatory care centers should proactively implement IP/IC measures, such as use of contact precautions, respiratory droplet precautions, cohorting of symptomatic individuals in a separate area or examination room, and enhanced surveillance for RTI symptoms among patients, HCW, and visitors, to reduce the spread of RTI or other transmissible infections throughout the facility.

Early identification of infectious threats in the ambulatory care setting can aid in the application of appropriate isolation or IC precautions. Screening of individuals for potential infection due to highly transmissible pathogens may be useful at the time of presentation to the outpatient facility. Specific syndromes involving diagnostic uncertainty such as RTI, diarrhea, or febrile rash are routinely encountered in outpatient settings and require appropriate triage. Although influenza is the most reported cause of RTI outbreaks, many respiratory viruses have emerged as significant causes of RTI in ambulatory outpatient settings. Severe acute respiratory syndrome 2 (SARS-CoV-2 or COVID-19), parainfluenza virus, human metapneumovirus, RSV, human adenovirus, and rhinoviruses all have been implicated in outbreaks of RTI in nursing homes, long- term care facilities and other ambulatory care settings. Individuals who meet screening criteria for potential infection should be directed to a separate entry to the facility, provided with a mask, if appropriate, and be separated from others as much as possible. When feasible, patients with rash or fever should be seen at times of low patient volume. During seasons of high respiratory infections, most notably COVID-19 and/or influenza, it is prudent to divide the patient waiting area into those with respiratory symptoms and those with no such symptoms.

Transmission-based precautions for MDROs or *C. difficile* infections may be implemented, depending on the complexity of patient care, susceptibility of the patient population to infection, and risk of spread. The presence of wounds and indwelling medical devices have been identified as risk factors for colonization with MDROs. Common risk factors for infection and colonization with *C. difficile* include frequent exposure to hospitals and antimicrobials, reduced gastric acid production from medications or underlying comorbidities, and age-related impairments in the immune response to the organism. Contact precautions should be considered preemptively during direct care of patients with these risk factors.

Emerging Infectious Diseases/ Reportable Diseases

Surveillance for HAIs, as described previously, is performed in both inpatient and outpatient settings. In addition to providing rates of infections that may be viewed over time, surveillance activities can also detect the emergence of new or unusual pathogens that trigger alarms at the time of first detection. Whereas most cHAIs involve common nosocomial pathogens including MRSA, VRE, *Enterobacterales, P. aeruginosa*, and *A. baumannii*, new infectious threats continue to emerge and spread, not only among inpatients but in the outpatient setting as well. Emerging and reemerging infectious diseases of particular concern include infections with antimicrobial-resistant pathogens, acute RTI, enteric diseases, vector-borne diseases and viral hemorrhagic fevers.

AMR is clearly a threat to critically ill inpatients and can be harmful in the outpatient setting. MDROs that may be transmitted in the ambulatory care environment include MRSA, VRE, ESBL- and CR-GNB, *C. difficile*, MDR-*M. tuberculosis*, and *C. auris*. The most significant risk factors for carriage of MDROs are presence of a urinary catheter, prior hospitalization, and presence of a wound or pressure ulcer. The fact that prior hospitalization was found to be a significant risk factor for the carriage of MDROs suggests that transfer between health care facilities may occur. Previous concerns regarding the transmission of problem MDRO pathogens such as *C. difficile*, MRSA, and ESBL-GNBs from the hospital to the community have been replaced by a broader understanding of a dynamic where pathogen flow is a two-way street where strains are recycled between facilities.

Acute RTI constitute the leading cause of communicable disease mortality worldwide. In addition to SARS-CoV-2, recent examples of emerging clinically important respiratory pathogens include human metapneumovirus, human bocavirus, Middle Eastern novel coronavirus associated with severe respiratory illness (MERS-CoV), pandemic influenza A (H1N1), and more virulent strains of avian influenza viruses (H5N1, H7N9). Public health authorities monitor novel influenza A viruses with pandemic potential as well as emerging variants of SARS-CoV-2. Concerning

SARS-CoV-2, active surveillance for asymptomatic individuals who may be shedding the virus has been widely adopted. Because a considerable number of individuals infected with SARS-CoV-2 may shed the virus and have been implicated in transmission events that occur prior to the onset of symptoms, testing for the virus in asymptomatic persons may help prevent nosocomial acquisition by allowing for early identification and appropriate transmission-based precautions.

Diarrheal diseases are second to acute RTI as causes of communicable disease mortality. The pathogens that cause enteric diseases are transmitted primarily by three routes—foodborne, waterborne, and person to person. In the ambulatory care setting the risk of person-to-person transmission is highest and contact precautions must be implemented. Enteric diseases of concern are those due to noroviruses, *C. difficile*, and MDR strains of *Salmonella* and *Campylobacter*. The emergence of cholera and identification of foodborne outbreaks of infection are periodic threats.

Vector-borne pathogens are those transmitted by insects and ticks. As such transmission in most ambulatory care settings is uncommon. Emerging vector-borne infections include those transmitted by mosquitos (e.g., dengue, Zika, yellow fever, chikungunya, and malaria) and ticks (e.g., Lyme disease, Rocky Mountain spotted fever, Heartland virus, and Bourbon virus diseases). Aside from yellow fever and Japanese encephalitis viruses, vaccines are not widely available for the vector-borne diseases, leaving vector control as the primary means of avoiding infection.

Outbreaks of viral hemorrhagic fevers due to Ebola and/or Marburg viruses have occurred multiple times in Africa and secondarily in other regions including the United States. Previously, it was thought that transmission of Ebola in health care settings could be prevented by adherence to basic infection control practices. Subsequent outbreaks, some involving "super spreader" events such as burial ceremonies, led to the use of more stringent control measures including use of PPE and disposal of potentially infectious items.

Systematic reporting of infectious diseases by clinicians and the CML has been mandated in the US for several years. A reportable disease is mandatory to report to state and territorial authorities when identified by a health care provider, hospital or laboratory. Each state has its own list of reportable diseases that may differ from those of other states and may vary over time. Examples of organisms requiring immediate reporting include *Neisseria meningitidis, Legionella*, acid-fast bacilli, and emerging MDROs, such as CR-GNBs, and *C. auris*. In addition, unusual pathogens (e.g., *Burkholderia pseudomallei*) or potential agents of bioterrorism (e.g., *Bacillus anthracis, Yersinia pestis*, and orthopox viruses) should be reported immediately to the IPP and any applicable state or local authorities. The organisms requiring immediate notification may vary from one institution to another.

Vaccines

Vaccination of patients, visitors, and HCWs is one of the cornerstones of preventing RTIs, including COVID-19 and influenza transmission in the ambulatory care setting. Immunization programs provide services that monitor immunity to vaccine-preventable diseases, including documentation of immunizations, record-keeping, and reporting to appropriate State and local immunization information systems. Effective immunization programs can (1) protect against vaccine-preventable infections among HCWs; (2) reduce the risk for transmission posed to other individuals in the outpatient (or inpatient) setting; (3) adhere to Advisory Committee on Immunization Practices recommendations as well as Federal, State, and local immunization requirements; (4) reduce the need for, and related costs associated with reactive measures, including postexposure prophylaxis, use of sick leave and work restrictions and (5) increase the efficiency of reporting immunizations of HCWs and others internally, as well as for performance reviews and quality improvement initiatives, and to external groups such as public health agencies.

For questions, see https://ebooks.health.elsevier.com

Supplemental Reading

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Questions

1. What are the Standard Precautions applied to infection prevention and control of -associated infections?
2. What is the most common means of case finding in HAI surveillance?
3. What is the major purpose of antimicrobial stewardship?
4. What is the main tenent of diagnostic stewardship?
5. What features of *Candida auris* make it a serious global threat?

Answers

1. Standard Precautions include hand hygiene, use of personal protective equipment (gloves, masks, gowns), respiratory/cough etiquette, sharps/injection safety.

2. Review of clinical microbiology laboratory data.

3. To optimize the use of antimicrobial agents to achieve the best outcomes while minimizing adverse events and limiting selection pressures that drive the emergence of resistance.

4. Diagnostic Stewardship should be used to increase test use in settings with a high probability of disease and to decrease test use in low probability settings where the potential for false-positive results may result in patient harm.

5. *C. auris* has shown the ability to survive on inanimate surfaces, prolonged colonization of infected or uninfected patients, transmission from patient to patient in health care environments, and a propensity to express resistance to multiple classes (azoles, echinocandins, and polyenes) of antifungal agents.

SECTION 2

General Principles of Laboratory Diagnosis