# THE NEW PLAGUES - NEW AND ANCIENT INFECTIOUS DISEASES THREATENING WORLD HEALTH



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# BIOL 342: The New Plagues - New and Ancient Infectious Diseases Threatening World Health (Hughes)

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# WEEK 1


## 1: An Invisible World

1.1: What Our Ancestors Knew

1.2: Systematic Approach

1.3: Types of Microorganisms

1.4: Review Questions


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# 1.1: What Our Ancestors Knew

**Learning Objectives**

- Describe how our ancestors improved food with the use of invisible microbes
- Describe how the causes of sickness and disease were explained in ancient times, prior to the invention of the microscope
- Describe key historical events associated with the birth of microbiology

Most people today, even those who know very little about microbiology, are familiar with the concept of microbes, or "germs," and their role in human health. Schoolchildren learn about bacteria, viruses, and other microorganisms, and many even view specimens under a microscope. But a few hundred years ago, before the invention of the microscope, the existence of many types of microbes was impossible to prove. By definition, **microorganisms**, or **microbes**, are very small organisms; many types of microbes are too small to see without a microscope, although some parasites and fungi are visible to the naked eye.

Humans have been living with—and using—microorganisms for much longer than they have been able to see them. Historical evidence suggests that humans have had some notion of microbial life since prehistoric times and have used that knowledge to develop foods as well as prevent and treat disease. In this section, we will explore some of the historical applications of microbiology as well as the early beginnings of microbiology as a science.

## Fermented Foods and Beverages

People across the world have enjoyed fermented foods and beverages like beer, wine, bread, yogurt, cheese, and pickled vegetables for all of recorded history. Discoveries from several archeological sites suggest that even prehistoric people took advantage of fermentation to preserve and enhance the taste of food. Archaeologists studying pottery jars from a Neolithic village in China found that people were making a fermented beverage from rice, honey, and fruit as early as 7000 BC.[1]

Production of these foods and beverages requires microbial fermentation, a process that uses bacteria, mold, or yeast to convert sugars (carbohydrates) to alcohol, gases, and organic acids (***Figure*** 1.1.1). While it is likely that people first learned about fermentation by accident—perhaps by drinking old milk that had curdled or old grape juice that had fermented—they later learned to harness the power of fermentation to make products like bread, cheese, and wine.

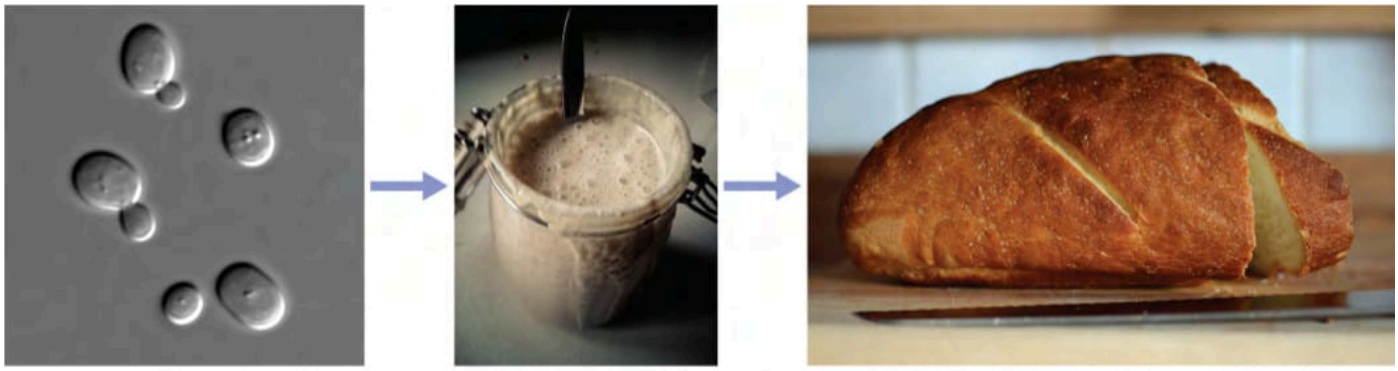



Figure 1.1.1: A microscopic view of *Saccharomyces cerevisiae*, the yeast responsible for making bread rise (left). Yeast is a microorganism. Its cells metabolize the carbohydrates in flour (middle) and produce carbon dioxide, which causes the bread to rise (right). (credit middle: modification of work by Janus Sandsgaard; credit right: modification of work by "MDreibelbis"/Flickr)

Clinical Focus

**Part 1**

Cora, a 41-year-old lawyer and mother of two, has recently been experiencing severe headaches, a high fever, and a stiff neck. Her husband, who has accompanied Cora to see a doctor, reports that Cora also seems confused at times and unusually drowsy. Based on these symptoms, the doctor suspects that Cora may have meningitis, a potentially life-threatening infection of the tissue that surrounds the brain and spinal cord.

Meningitis has several potential causes. It can be brought on by bacteria, fungi, viruses, or even a reaction to medication or exposure to heavy metals. Although people with viral meningitis usually heal on their own, bacterial and fungal meningitis are quite serious and require treatment.

Cora's doctor orders a lumbar puncture (spinal tap) to take three samples of cerebrospinal fluid (CSF) from around the spinal cord (***Figure*** 1.1.2). The samples will be sent to laboratories in three different departments for testing: clinical chemistry, microbiology, and hematology. The samples will first be visually examined to determine whether the CSF is abnormally colored or cloudy; then the CSF will be examined under a microscope to see if it contains a normal number of red and white blood cells and to check for any abnormal cell types. In the microbiology lab, the specimen will be centrifuged to concentrate any cells in a sediment; this sediment will be smeared on a slide and stained with a Gram stain. Gram staining is a procedure used to differentiate between two different types of bacteria (gram-positive and gram-negative).

About 80% of patients with bacterial meningitis will show bacteria in their CSF with a Gram stain[2] Cora's Gram stain did not show any bacteria, but her doctor decides to prescribe her antibiotics just in case. Part of the CSF sample will be cultured—put in special dishes to see if bacteria or fungi will grow. It takes some time for most microorganisms to reproduce in sufficient quantities to be detected and analyzed.

What types of microorganisms would be killed by antibiotic treatment?

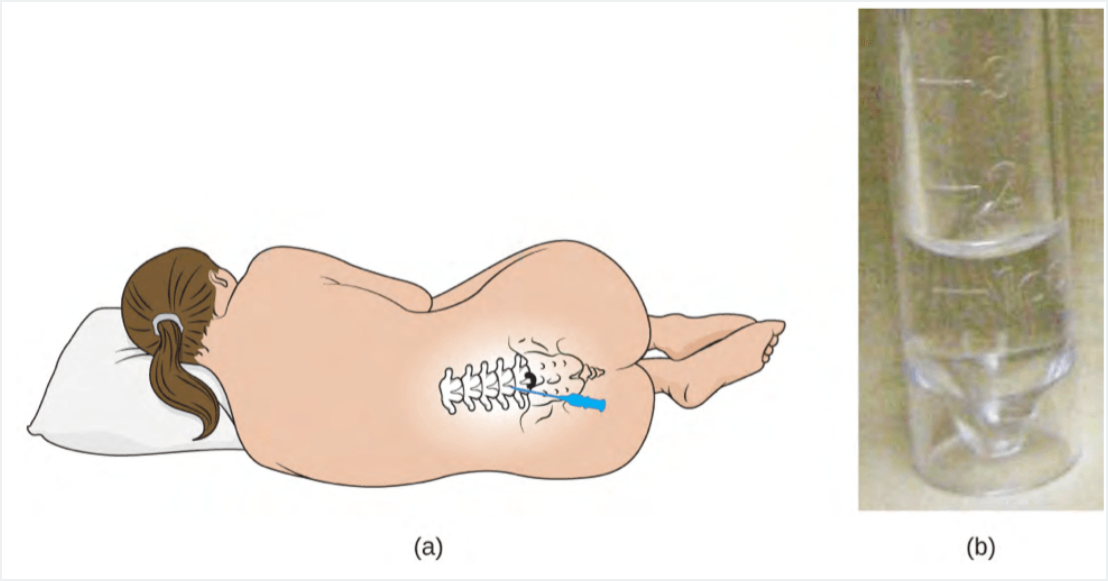



Figure 1.1.2: (a) A lumbar puncture is used to take a sample of a patient's cerebrospinal fluid (CSF) for testing. A needle is inserted between two vertebrae of the lower back, called the lumbar region. (b) CSF should be clear, as in this sample. Abnormally cloudy CSF may indicate an infection but must be tested further to confirm the presence of microorganisms. (credit a: modification of work by Centers for Disease Control and Prevention; credit b: modification of work by James Heilman

*Jump to the next Clinical Focus box.*

## The Iceman Treateth

Prehistoric humans had a very limited understanding of the causes of disease, and various cultures developed different beliefs

and explanations. While many believed that illness was punishment for angering the gods or was simply the result of fate, archaeological evidence suggests that prehistoric people attempted to treat illnesses and infections. One example of this is Ötzi the Iceman, a 5300-year-old mummy found frozen in the ice of the Ötzal Alps on the Austrian- Italian border in 1991. Because Ötzi was so well preserved by the ice, researchers discovered that he was infected with the eggs of the parasite Trichuris trichiura, which may have caused him to have abdominal pain and anemia. Researchers also found evidence of *Borrelia burgdorferi*, a bacterium that causes Lyme disease.[3] Some researchers think Ötzi may have been trying to treat his infections with the woody fruit of the *Piptoporus betulinus* fungus, which was discovered tied to his belongings.[4] This fungus has both laxative and antibiotic properties. Ötzi was also covered in tattoos that were made by cutting incisions into his skin, filling them with herbs, and then burning the herbs.[5] There is speculation that this may have been another attempt to treat his health ailments.

## Early Notions of Disease, Contagion, and Containment

Several ancient civilizations appear to have had some understanding that disease could be transmitted by things they could not see. This is especially evident in historical attempts to contain the spread of disease. For example, the Bible refers to the practice of quarantining people with leprosy and other diseases, suggesting that people understood that diseases could be communicable. Ironically, while leprosy is communicable, it is also a disease that progresses slowly. This means that people were likely quarantined after they had already spread the disease to others.

The ancient Greeks attributed disease to bad air, mal'aria, which they called "miasmatic odors." They developed hygiene practices that built on this idea. The Romans also believed in the miasma hypothesis and created a complex sanitation infrastructure to deal with sewage. In Rome, they built aqueducts, which brought fresh water into the city, and a giant sewer, the *Cloaca Maxima*, which carried waste away and into the river Tiber (***Figure*** 1.1.3). Some researchers believe that this infrastructure helped protect the Romans from epidemics of waterborne illnesses.

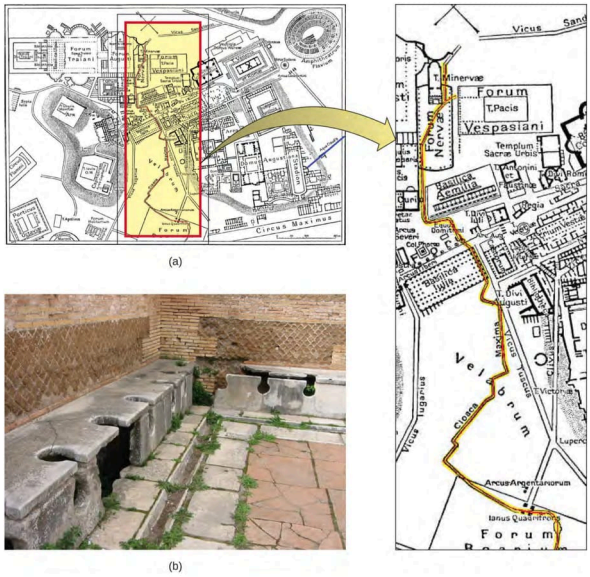



Figure 1.1.3: (a) The *Cloaca Maxima*, or "Greatest Sewer" (shown in red), ran through ancient Rome. It was an engineering marvel that carried waste away from the city and into the river Tiber. (b) These ancient latrines emptied into the *Cloaca Maxima*.

Even before the invention of the microscope, some doctors, philosophers, and scientists made great strides in understanding the invisible forces—what we now know as microbes—that can cause infection, disease, and death.

The Greek physician Hippocrates (460–370 BC) is considered the "father of Western medicine" (***Figure*** 1.1.4). Unlike many of his ancestors and contemporaries, he dismissed the idea that disease was caused by supernatural forces. Instead, he posited that diseases had natural causes from within patients or their environments. Hippocrates and his heirs are believed to have written the Hippocratic Corpus, a collection of texts that make up some of the oldest surviving medical books.[6] Hippocrates is also often credited as the author of the Hippocratic Oath, taken by new physicians to pledge their dedication to diagnosing and treating patients without causing harm.

While Hippocrates is considered the father of Western medicine, the Greek philosopher and historian Thucydides (460–395 BC) is considered the father of scientific history because he advocated for evidence-based analysis of cause-and-effect reasoning

(***Figure*** 1.1.4). Among his most important contributions are his observations regarding the Athenian plague that killed one-third of the population of Athens between 430 and 410 BC. Having survived the epidemic himself, Thucydides made the important observation that survivors did not get re-infected with the disease, even when taking care of actively sick people.[7] This observation shows an early understanding of the concept of immunity.

Marcus Terentius Varro (116–27 BC) was a prolific Roman writer who was one of the first people to propose the concept that things we cannot see (what we now call microorganisms) can cause disease (***Figure*** 1.1.4). In Res Rusticae (On Farming), published in 36 BC, he said that "precautions must also be taken in neighborhood swamps. . . because certain minute creatures [animalia minuta] grow there which cannot be seen by the eye, which float in the air and enter the body through the mouth and nose and there cause serious diseases."[8]

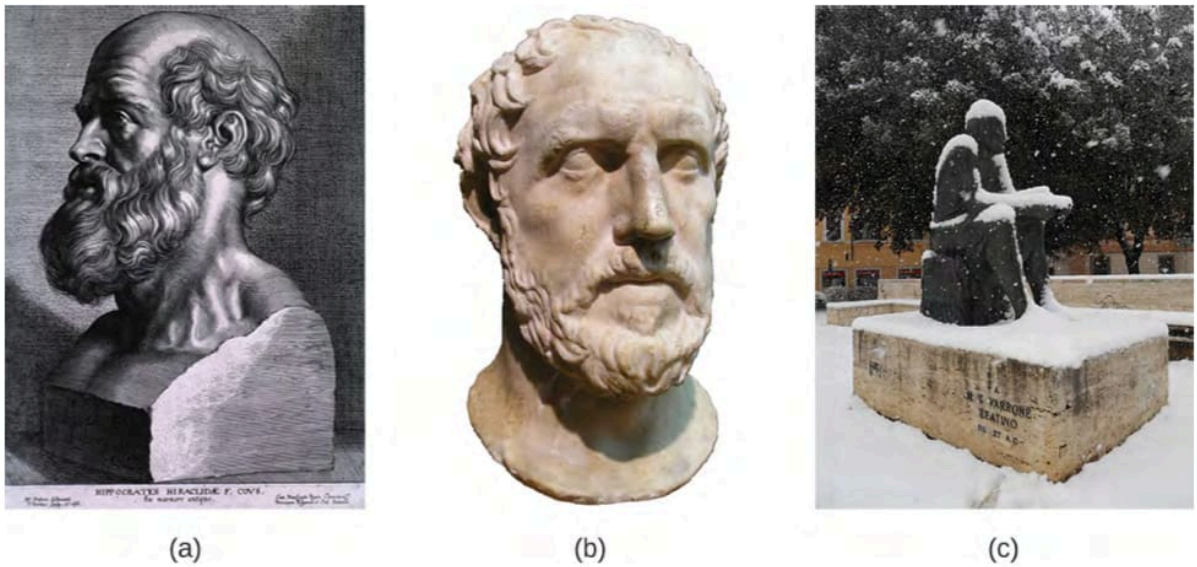



Figure 1.1.4: (a) Hippocrates, the "father of Western medicine," believed that diseases had natural, not supernatural, causes. (b) The historian Thucydides observed that survivors of the Athenian plague were subsequently immune to the infection. (c) Marcus Terentius Varro proposed that disease could be caused by "certain minute creatures . . . which cannot be seen by the eye." (credit c: modification of work by Alessandro Antonelli)

**Exercise 1.1.1**

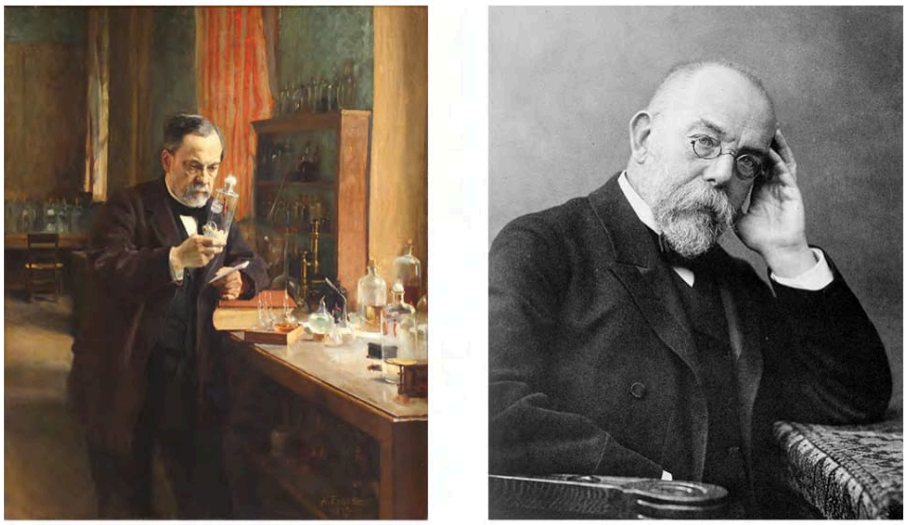
- Give two examples of foods that have historically been produced by humans with the aid of microbes.
- Explain how historical understandings of disease contributed to attempts to treat and contain disease.

## The Birth of Microbiology

While the ancients may have suspected the existence of invisible "minute creatures," it wasn't until the invention of the microscope that their existence was definitively confirmed. While it is unclear who exactly invented the microscope, a Dutch cloth merchant named Antonie van Leeuwenhoek (1632–1723) was the first to develop a lens powerful enough to view microbes. In 1675, using a simple but powerful microscope, Leeuwenhoek was able to observe single-celled organisms, which he described as "animalcules" or "wee little beasties," swimming in a drop of rain water. From his drawings of these little organisms, we now know he was looking at bacteria and protists. (We will explore Leeuwenhoek's contributions to microscopy further in How We See the Invisible World.)

Nearly 200 years after van Leeuwenhoek got his first glimpse of microbes, the "Golden Age of Microbiology" spawned a host of new discoveries between 1857 and 1914. Two famous microbiologists, Louis Pasteur and Robert Koch, were especially active in advancing our understanding of the unseen world of microbes (***Figure*** 1.1.5). Pasteur, a French chemist, showed that individual microbial strains had unique properties and demonstrated that fermentation is caused by microorganisms. He also invented pasteurization, a process used to kill microorganisms responsible for spoilage, and developed vaccines for the treatment of diseases, including rabies, in animals and humans. Koch, a German physician, was the first to demonstrate the connection between a single, isolated microbe and a known human disease. For example, he discovered the bacteria that cause anthrax

(*Bacillus anthracis*), cholera (*Vibrio cholera*), and tuberculosis (*Mycobacterium tuberculosis*).[9] We will discuss these famous microbiologists, and others, in later chapters.



(a) (b)

Figure 1.1.5: (a) Louis Pasteur (1822–1895) is credited with numerous innovations that advanced the fields of microbiology and immunology. (b) Robert Koch (1843–1910) identified the specific microbes that cause anthrax, cholera, and tuberculosis.

As microbiology has developed, it has allowed the broader discipline of biology to grow and flourish in previously unimagined ways. Much of what we know about human cells comes from our understanding of microbes, and many of the tools we use today to study cells and their genetics derive from work with microbes.

## Exercise 1.1.2

- How did the discovery of microbes change human understanding of disease?

## Micro Connections

**Microbiology Toolbox**

Because individual microbes are generally too small to be seen with the naked eye, the science of microbiology is dependent on technology that can artificially enhance the capacity of our natural senses of perception. Early microbiologists like Pasteur and Koch had fewer tools at their disposal than are found in modern laboratories, making their discoveries and innovations that much more impressive. Later chapters of this text will explore many applications of technology in depth, but for now, here is a brief overview of some of the fundamental tools of the microbiology lab.

- **Microscopes** produce magnified images of microorganisms, human cells and tissues, and many other types of specimens too small to be observed with the naked eye.
- **Stains and dyes** are used to add color to microbes so they can be better observed under a microscope. Some dyes can be used on living microbes, whereas others require that the specimens be fixed with chemicals or heat before staining. Some stains only work on certain types of microbes because of differences in their cellular chemical composition.
- **Growth media** are used to grow microorganisms in a lab setting. Some media are liquids; others are more solid or gel-like. A growth medium provides nutrients, including water, various salts, a source of carbon (like glucose), and a source of nitrogen and amino acids (like yeast extract) so microorganisms can grow and reproduce. Ingredients in a growth medium can be modified to grow unique types of microorganisms.
- **A Petri dish** is a flat-lidded dish that is typically 10–11 centimeters (cm) in diameter and 1–1.5 cm high. Petri dishes made out of either plastic or glass are used to hold growth media (***Figure*** 1.1.6).

- **Test tubes** are cylindrical plastic or glass tubes with rounded bottoms and open tops. They can be used to grow microbes in broth, or semisolid or solid growth media.
- A **Bunsen burner** is a metal apparatus that creates a flame that can be used to sterilize pieces of equipment. A rubber tube carries gas (fuel) to the burner. In many labs, Bunsen burners are being phased out in favor of infrared microincinerators, which serve a similar purpose without the safety risks of an open flame.
- An **inoculation loop** is a handheld tool that ends in a small wire loop (***Figure*** 1.1.6). The loop can be used to streak microorganisms on agar in a Petri dish or to transfer them from one test tube to another. Before each use, the inoculation loop must be sterilized so cultures do not become contaminated.

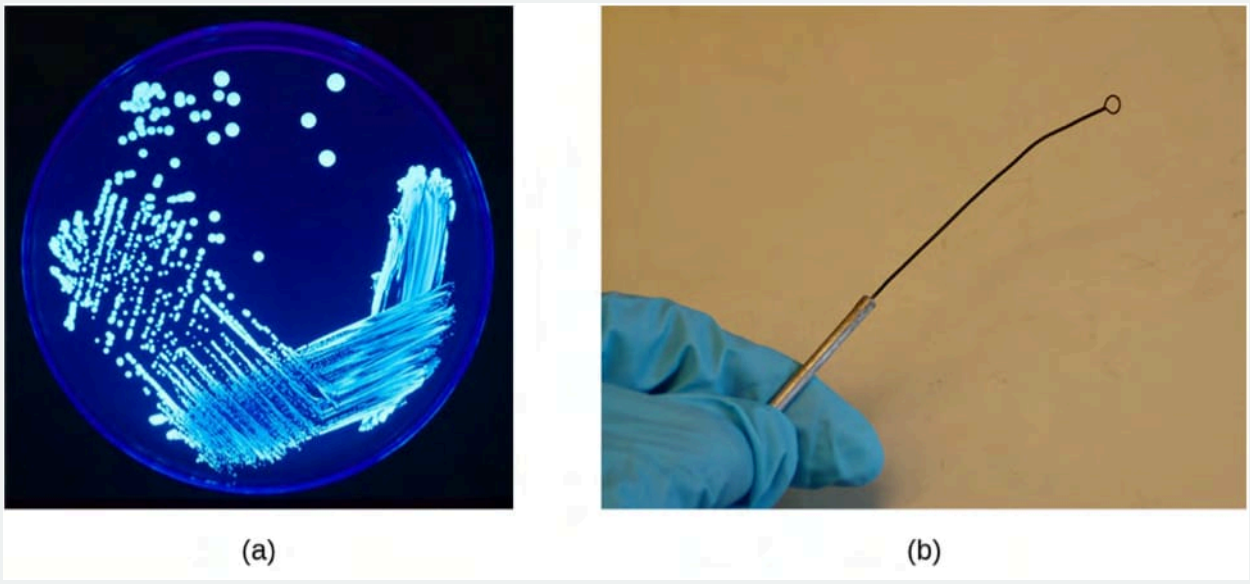



Figure 1.1.6: (a) This Petri dish filled with agar has been streaked with *Legionella*, the bacterium responsible for causing Legionnaire's disease. (b) An inoculation loop like this one can be used to streak bacteria on agar in a Petri dish. (credit a: modification of work by Centers for Disease Control and Prevention; credit b: modification of work by Jeffrey M. Vinocur)

## Key Concepts and Summary

- **Microorganisms** (or **microbes**) are living organisms that are generally too small to be seen without a microscope.
- Throughout history, humans have used microbes to make fermented foods such as beer, bread, cheese, and wine.
- Long before the invention of the microscope, some people theorized that infection and disease were spread by living things that were too small to be seen. They also correctly intuited certain principles regarding the spread of disease and immunity.
- Antonie van Leeuwenhoek, using a microscope, was the first to actually describe observations of bacteria, in 1675.
- During the Golden Age of Microbiology (1857–1914), microbiologists, including Louis Pasteur and Robert Koch, discovered many new connections between the fields of microbiology and medicine.

## Footnotes


1. P.E. McGovern et al. "Fermented Beverages of Pre- and Proto-Historic China." *Proceedings of the National Academy of Sciences of the United States of America* 1 no. 51 (2004):17593–17598. doi:10.1073/pnas.0407921102.
2. Rebecca Buxton. "Examination of Gram Stains of Spinal Fluid—Bacterial Meningitis." *American Society for Microbiology*. 2007. http://www.microbelibrary.org/librar...ial-meningitis
3. A. Keller et al. "New Insights into the Tyrolean Iceman's Origin and Phenotype as Inferred by Whole-Genome Sequencing." *Nature Communications*, 3 (2012): 698. doi:10.1038/ncomms1701.
4. L. Capasso. "5300 Years Ago, the Ice Man Used Natural Laxatives and Antibiotics." *The Lancet*, 352 (1998) 9143: 1864. doi: 10.1016/ s0140-6736(05)79939-6.
5. L. Capasso, L. "5300 Years Ago, the Ice Man Used Natural Laxatives and Antibiotics." *The Lancet*, 352 no. 9143 (1998): 1864. doi: 10.1016/s0140-6736(05)79939-6.
6. G. Pappas et al. "Insights Into Infectious Disease in the Era of Hippocrates." *International Journal of Infectious Diseases* 12 (2008) 4:347–350. doi: http://dx.doi.org/10.1016/j.ijid.2007.11.003.
7. Thucydides. *The History of the Peloponnesian War.* The Second Book. 431 BC. Translated by Richard Crawley.

http://classics.mit.edu/Thucydides/pelopwar.2.second.html.
8. Plinio Prioreschi. *A History of Medicine: Roman Medicine.* Lewiston, NY: Edwin Mellen Press, 1998: p. 215.
9. S.M. Blevins and M.S. Bronze. "Robert Koch and the 'Golden Age' of Bacteriology." *International Journal of Infectious Diseases.* 14 no. 9 (2010): e744-e751. doi:10.1016/j.ijid.2009.12.003.

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# 1.2: Systematic Approach

**Learning Objectives**

- Describe how microorganisms are classified and distinguished as unique species
- Compare historical and current systems of taxonomy used to classify microorganisms

Once microbes became visible to humans with the help of microscopes, scientists began to realize their enormous diversity. Microorganisms vary in all sorts of ways, including their size, their appearance, and their rates of reproduction. To study this incredibly diverse new array of organisms, researchers needed a way to systematically organize them.

## The Science of Taxonomy

**Taxonomy** is the classification, description, identification, and naming of living organisms. Classification is the practice of organizing organisms into different groups based on their shared characteristics. The most famous early taxonomist was a Swedish botanist, zoologist, and physician named Carolus Linnaeus (1701–1778). In 1735, Linnaeus published Systema Naturae, an 11-page booklet in which he proposed the Linnaean taxonomy, a system of categorizing and naming organisms using a standard format so scientists could discuss organisms using consistent terminology. He continued to revise and add to the book, which grew into multiple volumes (***Figure*** 1.2.1).



Figure 1.2.1: Swedish botanist, zoologist, and physician Carolus Linnaeus developed a new system for categorizing plants and animals. In this 1853 portrait by Hendrik Hollander, Linnaeus is holding a twinflower, named *Linnaea borealis* in his honor.

In his taxonomy, Linnaeus divided the natural world into three kingdoms: animal, plant, and mineral (the mineral kingdom was later abandoned). Within the animal and plant kingdoms, he grouped organisms using a hierarchy of increasingly specific levels and sublevels based on their similarities. The names of the levels in Linnaeus's original taxonomy were kingdom, class, order, family, genus (plural: genera), and species. Species was, and continues to be, the most specific and basic taxonomic unit.

## Evolving Trees of Life (Phylogenies)

With advances in technology, other scientists gradually made refinements to the Linnaean system and eventually created new systems for classifying organisms. In the 1800s, there was a growing interest in developing taxonomies that took into account the evolutionary relationships, or **phylogenies**, of all different species of organisms on earth. One way to depict these relationships is via a diagram called a phylogenetic tree (or tree of life). In these diagrams, groups of organisms are arranged by how closely

related they are thought to be. In early phylogenetic trees, the relatedness of organisms was inferred by their visible similarities, such as the presence or absence of hair or the number of limbs. Now, the analysis is more complicated. Today, phylogenic analyses include genetic, biochemical, and embryological comparisons, as will be discussed later in this chapter.

Linnaeus's tree of life contained just two main branches for all living things: the animal and plant kingdoms. In 1866, Ernst Haeckel, a German biologist, philosopher, and physician, proposed another kingdom, Protista, for unicellular organisms (***Figure*** 1.2.2). He later proposed a fourth kingdom, Monera, for unicellular organisms whose cells lack nuclei, like bacteria.

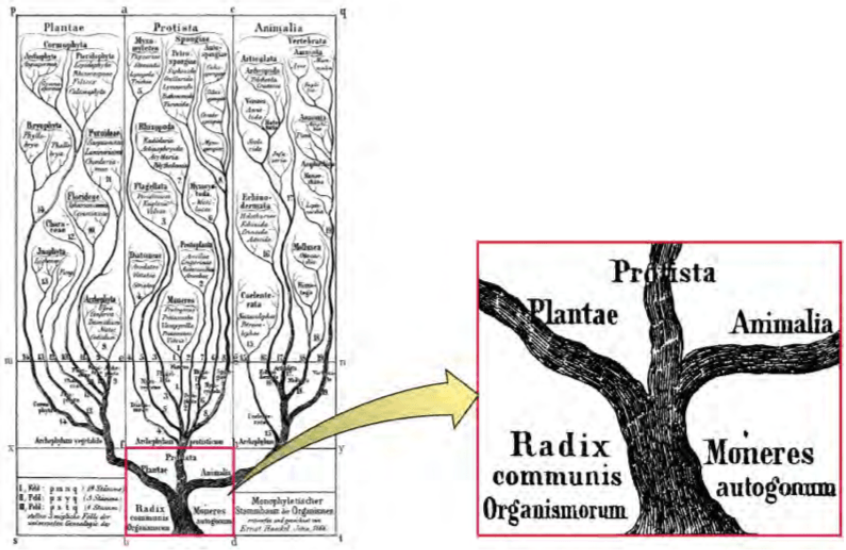



Figure 1.2.2: Ernst Haeckel's rendering of the tree of life, from his 1866 book *General Morphology of Organisms*, contained three kingdoms: Plantae, Protista, and Animalia. He later added a fourth kingdom, Monera, for unicellular organisms lacking a nucleus.

Nearly 100 years later, in 1969, American ecologist Robert Whittaker (1920–1980) proposed adding another kingdom—Fungi—in his tree of life. Whittaker's tree also contained a level of categorization above the kingdom level—the empire or superkingdom level—to distinguish between organisms that have membrane-bound nuclei in their cells (eukaryotes) and those that do not (prokaryotes). Empire Prokaryota contained just the Kingdom Monera. The Empire Eukaryota contained the other four kingdoms: Fungi, Protista, Plantae, and Animalia. Whittaker's five-kingdom tree was considered the standard phylogeny for many years.

***Figure*** 1.2.3 shows how the tree of life has changed over time. Note that viruses are not found in any of these trees. That is because they are not made up of cells and thus it is difficult to determine where they would fit into a tree of life.

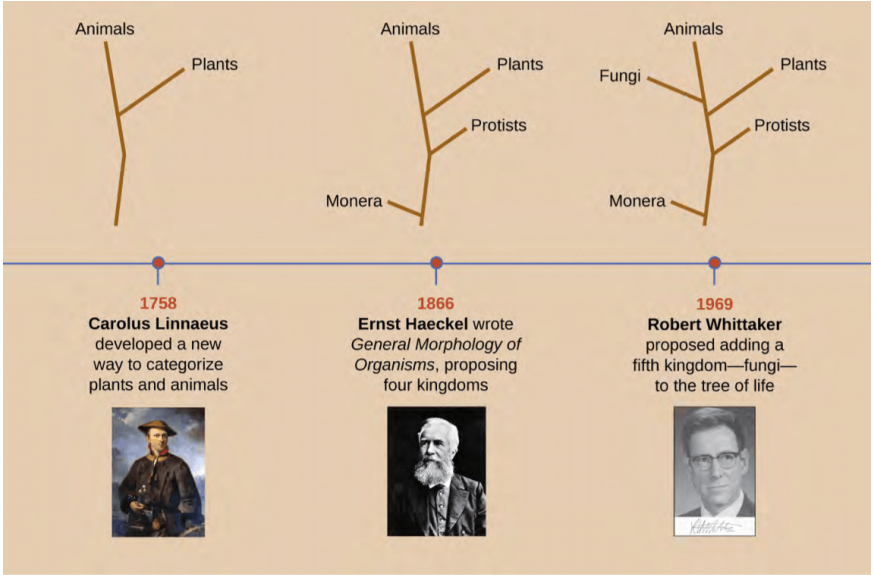



Figure 1.2.3: This timeline shows how the shape of the tree of life has changed over the centuries. Even today, the taxonomy of living organisms is continually being reevaluated and refined with advances in technology.

## Exercise 1.2.1

- Briefly summarize how our evolving understanding of microorganisms has contributed to changes in the way that organisms are classified

## Clinical Focus

**Part 2**

Antibiotic drugs are specifically designed to kill or inhibit the growth of bacteria. But after a couple of days on antibiotics, Cora shows no signs of improvement. Also, her CSF cultures came back from the lab negative. Since bacteria or fungi were not isolated from Cora's CSF sample, her doctor rules out bacterial and fungal meningitis. Viral meningitis is still a possibility.

However, Cora now reports some troubling new symptoms. She is starting to have difficulty walking. Her muscle stiffness has spread from her neck to the rest of her body, and her limbs sometimes jerk involuntarily. In addition, Cora's cognitive symptoms are worsening. At this point, Cora's doctor becomes very concerned and orders more tests on the CSF samples.

- What types of microorganisms could be causing Cora's symptoms?

*Jump to the next Clinical Focus box. Go back to the previous Clinical Focus box*

## The Role of Genetics in Modern Taxonomy

Haeckel's and Whittaker's trees presented hypotheses about the phylogeny of different organisms based on readily observable characteristics. But the advent of molecular genetics in the late 20th century revealed other ways to organize phylogenetic trees. Genetic methods allow for a standardized way to compare all living organisms without relying on observable characteristics that can often be subjective. Modern taxonomy relies heavily on comparing the nucleic acids (deoxyribonucleic acid [DNA] or ribonucleic acid [RNA]) or proteins from different organisms. The more similar the nucleic acids and proteins are between two organisms, the more closely related they are considered to be.

In the 1970s, American microbiologist Carl Woese discovered what appeared to be a "living record" of the evolution of organisms. He and his collaborator George Fox created a genetics-based tree of life based on similarities and differences they observed in the small subunit ribosomal RNA (rRNA) of different organisms. In the process, they discovered that a certain type of bacteria, called archaebacteria (now known simply as archaea), were significantly different from other bacteria and eukaryotes in terms of

the sequence of small subunit rRNA. To accommodate this difference, they created a tree with three Domains above the level of Kingdom: Archaea, Bacteria, and Eukarya (***Figure*** 1.2.4). Genetic analysis of the small subunit rRNA suggests archaea, bacteria, and eukaryotes all evolved from a common ancestral cell type. The tree is skewed to show a closer evolutionary relationship between Archaea and Eukarya than they have to Bacteria.

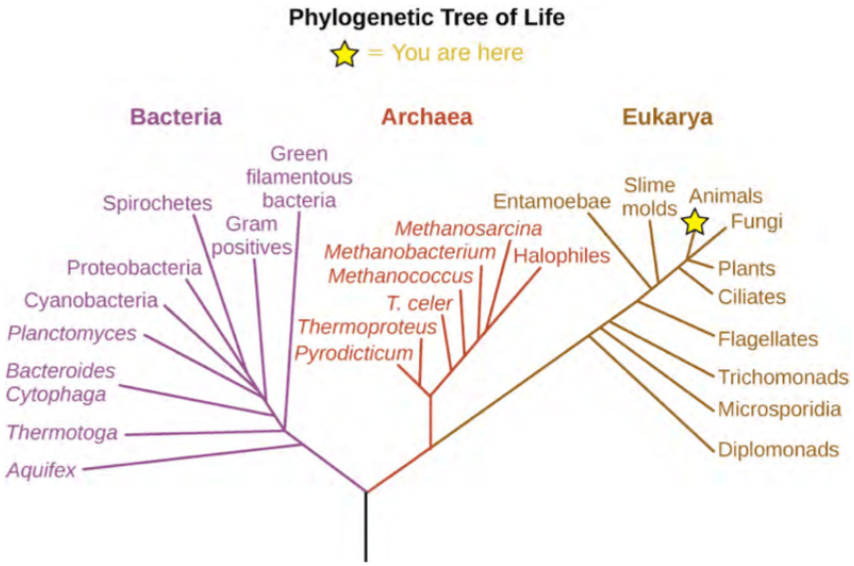



Figure 1.2.4: Woese and Fox's phylogenetic tree contains three domains: Bacteria, Archaea, and Eukarya. Domains Archaea and Bacteria contain all prokaryotic organisms, and Eukarya contains all eukaryotic organisms. (credit: modification of work by Eric Gaba)

Scientists continue to use analysis of RNA, DNA, and proteins to determine how organisms are related. One interesting, and complicating, discovery is that of horizontal gene transfer—when a gene of one species is absorbed into another organism's genome. Horizontal gene transfer is especially common in microorganisms and can make it difficult to determine how organisms are evolutionarily related. Consequently, some scientists now think in terms of "webs of life" rather than "trees of life."

**Exercise 1.2.2**

- In modern taxonomy, how do scientists determine how closely two organisms are related?
- Explain why the branches on the "tree of life" all originate from a single "trunk."

## Naming Microbes

In developing his taxonomy, Linnaeus used a system of binomial nomenclature, a two-word naming system for identifying organisms by genus and species. For example, modern humans are in the genus Homo and have the species name sapiens, so their scientific name in binomial nomenclature is Homo sapiens. In binomial nomenclature, the genus part of the name is always capitalized; it is followed by the species name, which is not capitalized. Both names are italicized.

Taxonomic names in the 18th through 20th centuries were typically derived from Latin, since that was the common language used by scientists when taxonomic systems were first created. Today, newly discovered organisms can be given names derived from Latin, Greek, or English. Sometimes these names reflect some distinctive trait of the organism; in other cases, microorganisms are named after the scientists who discovered them. The archaeonHaloquadratum walsbyi is an example of both of these naming schemes. The genus, Haloquadratum, describes the microorganism's saltwater habitat (halo is derived from the Greek word for "salt") as well as the arrangement of its square cells, which are arranged in square clusters of four cells (quadratum is Latin for "foursquare"). The species, walsbyi, is named after Anthony Edward Walsby, the microbiologist who discovered Haloquadratum walsbyi in in 1980. While it might seem easier to give an organism a common descriptive name—like a red-headed woodpecker—we can imagine how that could become problematic. What happens when another species of woodpecker with red head coloring is discovered? The systematic nomenclature scientists use eliminates this potential problem by assigning each organism a single, unique two-word name that is recognized by scientists all over the world.

In this text, we will typically abbreviate an organism's genus and species after its first mention. The abbreviated form is simply

the first initial of the genus, followed by a period and the full name of the species. For example, the bacterium Escherichia coli is shortened to E. coli in its abbreviated form. You will encounter this same convention in other scientific texts as well.

## Bergey's Manuals

Whether in a tree or a web, microbes can be difficult to identify and classify. Without easily observable macroscopic features like feathers, feet, or fur, scientists must capture, grow, and devise ways to study their biochemical properties to differentiate and classify microbes. Despite these hurdles, a group of microbiologists created and updated a set of manuals for identifying and classifying microorganisms. First published in 1923 and since updated many times, *Bergey's Manual of Determinative Bacteriology* and *Bergey's Manual of Systematic Bacteriology* are the standard references for identifying and classifying different prokaryotes. (Appendix D of this textbook is partly based on Bergey's manuals; it shows how the organisms that appear in this textbook are classified.) Because so many bacteria look identical, methods based on nonvisual characteristics must be used to identify them. For example, biochemical tests can be used to identify chemicals unique to certain species. Likewise, serological tests can be used to identify specific antibodies that will react against the proteins found in certain species. Ultimately, DNA and rRNA sequencing can be used both for identifying a particular bacterial species and for classifying newly discovered species.

### Exercise 1.2.3

- What is binomial nomenclature and why is it a useful tool for naming organisms?
- Explain why a resource like one of Bergey's manuals would be helpful in identifying a microorganism in a sample.

### Micro Connections

**Same Name, Different Strain**

Within one species of microorganism, there can be several subtypes called strains. While different strains may be nearly identical genetically, they can have very different attributes. The bacterium *Escherichia coli* is infamous for causing food poisoning and traveler's diarrhea. However, there are actually many different strains of *E. coli*, and they vary in their ability to cause disease.

One pathogenic (disease-causing) *E. coli* strain that you may have heard of is *E. coli* O157:H7. In humans, infection from *E. coli* O157:H7 can cause abdominal cramps and diarrhea. Infection usually originates from contaminated water or food, particularly raw vegetables and undercooked meat. In the 1990s, there were several large outbreaks of *E. coli* O157:H7 thought to have originated in undercooked hamburgers.

While *E. coli* O157:H7 and some other strains have given *E. coli* a bad name, most *E. coli* strains do not cause disease. In fact, some can be helpful. Different strains of *E. coli* found naturally in our gut help us digest our food, provide us with some needed chemicals, and fight against pathogenic microbes.

### Link to Learning

Learn more about phylogenetic trees by exploring the Wellcome Trust's interactive Tree of Life. The **website** contains information, photos, and animations about many different organisms. Select two organisms to see how they are evolutionarily related.

# Key Concepts and Summary

- Carolus Linnaeus developed a taxonomic system for categorizing organisms into related groups.
- **Binomial nomenclature** assigns organisms Latinized scientific names with a genus and species designation.
- A **phylogenetic tree** is a way of showing how different organisms are thought to be related to one another from an evolutionary standpoint.
- The first phylogenetic tree contained kingdoms for plants and animals; Ernst Haeckel proposed adding kingdom for protists.
- Robert Whittaker's tree contained five kingdoms: Animalia, Plantae, Protista, Fungi, and Monera.

- Carl Woese used small subunit ribosomal RNA to create a phylogenetic tree that groups organisms into three
- domains based on their genetic similarity.
- Bergey's manuals of determinative and systemic bacteriology are the standard references for identifying and classifying bacteria, respectively.
- Bacteria can be identified through biochemical tests, DNA/RNA analysis, and serological testing methods.

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# 1.3: Types of Microorganisms

## Learning Objectives

- List the various types of microorganisms and describe their defining characteristics
- Give examples of different types of cellular and viral microorganisms and infectious agents
- Describe the similarities and differences between archaea and bacteria
- Provide an overview of the field of microbiology

Most microbes are unicellular and small enough that they require artificial magnification to be seen. However, there are some unicellular microbes that are visible to the naked eye, and some multicellular organisms that are microscopic. An object must measure about 100 micrometers (μm) to be visible without a microscope, but most microorganisms are many times smaller than that. For some perspective, consider that a typical animal cell measures roughly 10 μm across but is still microscopic. Bacterial cells are typically about 1 μm, and viruses can be 10 times smaller than bacteria (***Figure*** 1.3.1). See Table 1.3.1 for units of length used in microbiology.

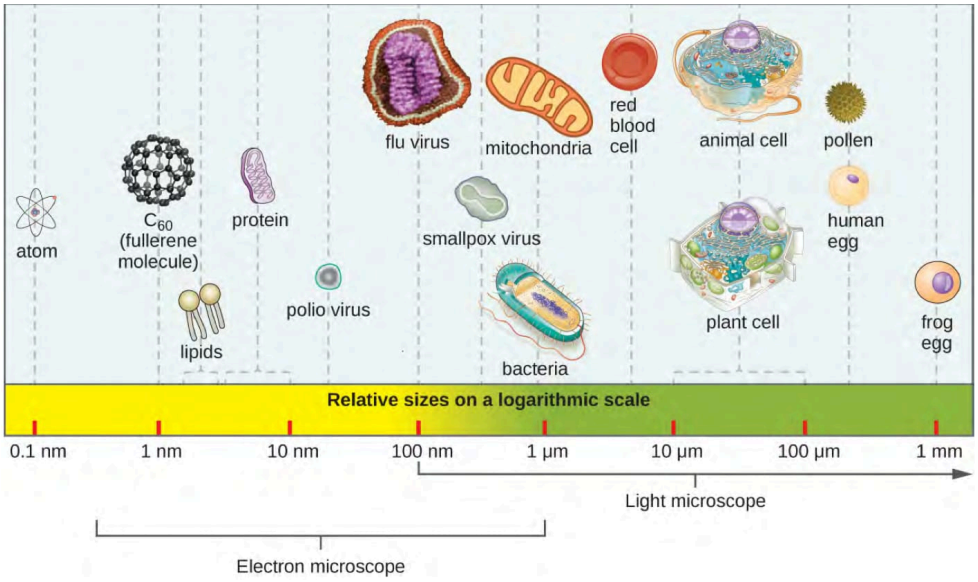



Figure 1.3.1: The relative sizes of various microscopic and nonmicroscopic objects. Note that a typical virus measures about 100 nm, 10 times smaller than a typical bacterium (~1 μm), which is at least 10 times smaller than a typical plant or animal cell (~10–100 μm). An object must measure about 100 μm to be visible without a microscope.

*Table 1.3.1: Units of Length Commonly Used in Microbiology*

| Metric Unit | Meaning of Prefix | Metric Equivalent |
|---|---|---|
| meter (m) | — | 1 m = $10^0$ m |
| decimeter (dm) | 1/10 | 1 dm = 0.1 m = $10^{-1}$ m |
| centimeter (cm) | 1/100 | 1 cm = 0.01 m = $10^{-2}$ m |
| millimeter (mm) | 1/1000 | 1 mm = 0.001 m = $10^{-3}$ m |
| micrometer (μm) | 1/1,000,000 | 1 μm = 0.000001 m = $10^{-6}$ m |
| nanometer (nm) | 1/1,000,000,000 | 1 nm = 0.000000001 m = $10^{-9}$ m |

Microorganisms differ from each other not only in size, but also in structure, habitat, metabolism, and many other characteristics.

While we typically think of microorganisms as being unicellular, there are also many multicellular organisms that are too small to be seen without a microscope. Some microbes, such as viruses, are even acellular (not composed of cells).

Microorganisms are found in each of the three domains of life: Archaea, Bacteria, and Eukarya. Microbes within the domains Bacteria and Archaea are all prokaryotes (their cells lack a nucleus), whereas microbes in the domain Eukarya are eukaryotes (their cells have a nucleus). Some microorganisms, such as viruses, do not fall within any of the three domains of life. In this section, we will briefly introduce each of the broad groups of microbes. Later chapters will go into greater depth about the diverse species within each group.

**Link to Learning**

How big is a bacterium or a virus compared to other objects? Check out this interactive website to get a feel for the scale of different microorganisms.

## Prokaryotic Microorganisms

**Bacteria** are found in nearly every habitat on earth, including within and on humans. Most bacteria are harmless or helpful, but some are **pathogens**, causing disease in humans and other animals. Bacteria are prokaryotic because their genetic material (DNA) is not housed within a true nucleus. Most bacteria have cell walls that contain peptidoglycan.

Bacteria are often described in terms of their general shape. Common shapes include spherical (coccus), rod-shaped (bacillus), or curved (spirillum, spirochete, or vibrio). ***Figure*** 1.3.2 shows examples of these shapes.

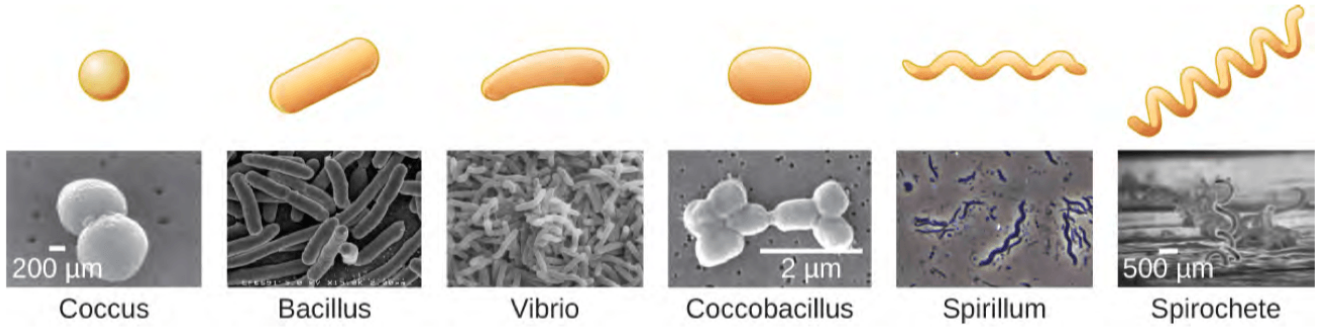



Figure 1.3.2: Common bacterial shapes. Note how coccobacillus is a combination of spherical (coccus) and rod- shaped (bacillus). (credit "Coccus": modification of work by Janice Haney Carr, Centers for Disease Control and Prevention; credit "Coccobacillus": modification of work by Janice Carr, Centers for Disease Control and Prevention; credit "Spirochete": Centers for Disease Control and Prevention)

They have a wide range of metabolic capabilities and can grow in a variety of environments, using different combinations of nutrients. Some bacteria are photosynthetic, such as oxygenic cyanobacteria and anoxygenic green sulfur and green nonsulfur bacteria; these bacteria use energy derived from sunlight, and fix carbon dioxide for growth. Other types of bacteria are nonphotosynthetic, obtaining their energy from organic or inorganic compounds in their environment.

**Archaea** are also unicellular prokaryotic organisms. Archaea and bacteria have different evolutionary histories, as well as significant differences in genetics, metabolic pathways, and the composition of their cell walls and membranes. Unlike most bacteria, archaeal cell walls do not contain peptidoglycan, but their cell walls are often composed of a similar substance called pseudopeptidoglycan. Like bacteria, archaea are found in nearly every habitat on earth, even extreme environments that are very cold, very hot, very basic, or very acidic (***Figure*** 1.3.3). Some archaea live in the human body, but none have been shown to be human pathogens.



Figure 1.3.3: Some archaea live in extreme environments, such as the Morning Glory pool, a hot spring in Yellowstone National Park. The color differences in the pool result from the different communities of microbes that are able to thrive at various water temperatures.

**Exercise 1.3.1**

- What are the two main types of prokaryotic organisms?
- Name some of the defining characteristics of each type

## Eukaryotic Microorganisms

The domain Eukarya contains all eukaryotes, including uni- or multicellular eukaryotes such as protists, fungi, plants, and animals. The major defining characteristic of eukaryotes is that their cells contain a nucleus.

### Protists

**Protists** are unicellular eukaryotes that are not plants, animals, or fungi. Algae and protozoa are examples of protists.

**Algae** (singular: alga) are plant-like protists that can be either unicellular or multicellular (***Figure*** 1.3.4). Their cells are surrounded by cell walls made of cellulose, a type of carbohydrate. Algae are photosynthetic organisms that extract energy from the sun and release oxygen and carbohydrates into their environment. Because other organisms can use their waste products for energy, algae are important parts of many ecosystems. Many consumer products contain ingredients derived from algae, such as carrageenan or alginic acid, which are found in some brands of ice cream, salad dressing, beverages, lipstick, and toothpaste. A derivative of algae also plays a prominent role in the microbiology laboratory. Agar, a gel derived from algae, can be mixed with various nutrients and used to grow microorganisms in a Petri dish. Algae are also being developed as a possible source for biofuels.

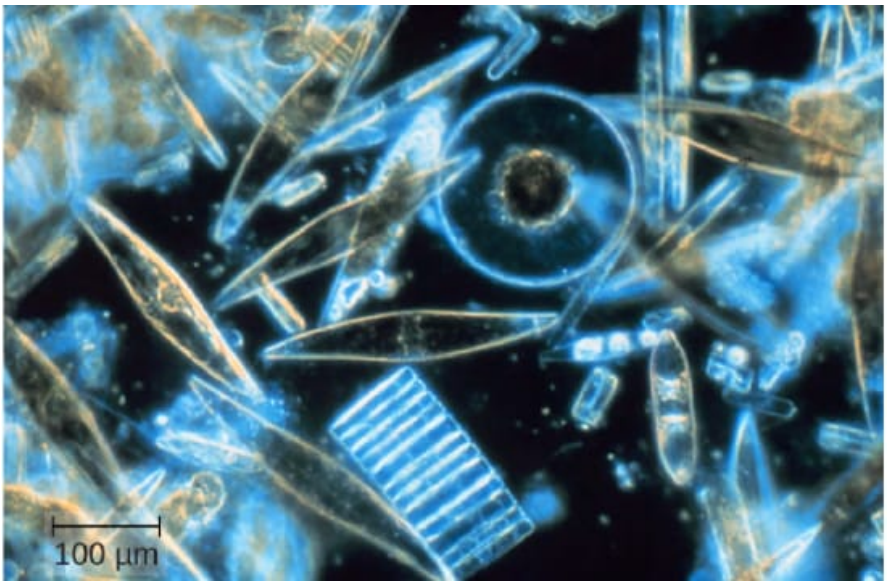



Figure 1.3.4: Assorted diatoms, a kind of algae, live in annual sea ice in McMurdo Sound, Antarctica. Diatoms range in size from 2 µm to 200 µm and are visualized here using light microscopy. (credit: modification of work by National Oceanic and Atmospheric Administration)

**Protozoa** (singular: protozoan) are protists that make up the backbone of many food webs by providing nutrients for other organisms. Protozoa are very diverse. Some protozoa move with help from hair-like structures called cilia or whip-like structures called flagella. Others extend part of their cell membrane and cytoplasm to propel themselves forward. These cytoplasmic extensions are called pseudopods ("false feet"). Some protozoa are photosynthetic; others feed on organic material. Some are free-living, whereas others are parasitic, only able to survive by extracting nutrients from a host organism. Most protozoa are harmless, but some are pathogens that can cause disease in animals or humans (***Figure*** 1.3.5).

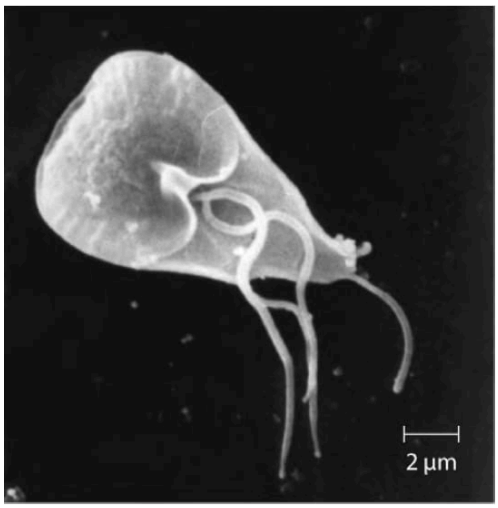



Figure 1.3.5: *Giardia lamblia*, an intestinal protozoan parasite that infects humans and other mammals, causing severe diarrhea. (credit: modification of work by Centers for Disease Control and Prevention)

## Fungi

**Fungi** (singular: fungus) are also eukaryotes. Some multicellular fungi, such as mushrooms, resemble plants, but they are actually quite different. Fungi are not photosynthetic, and their cell walls are usually made out of chitin rather than cellulose.

Unicellular fungi—yeasts—are included within the study of microbiology. There are more than 1000 known species. Yeasts are found in many different environments, from the deep sea to the human navel. Some yeasts have beneficial uses, such as causing bread to rise and beverages to ferment; but yeasts can also cause food to spoil. Some even cause diseases, such as vaginal yeast infections and oral thrush (***Figure*** 1.3.6).

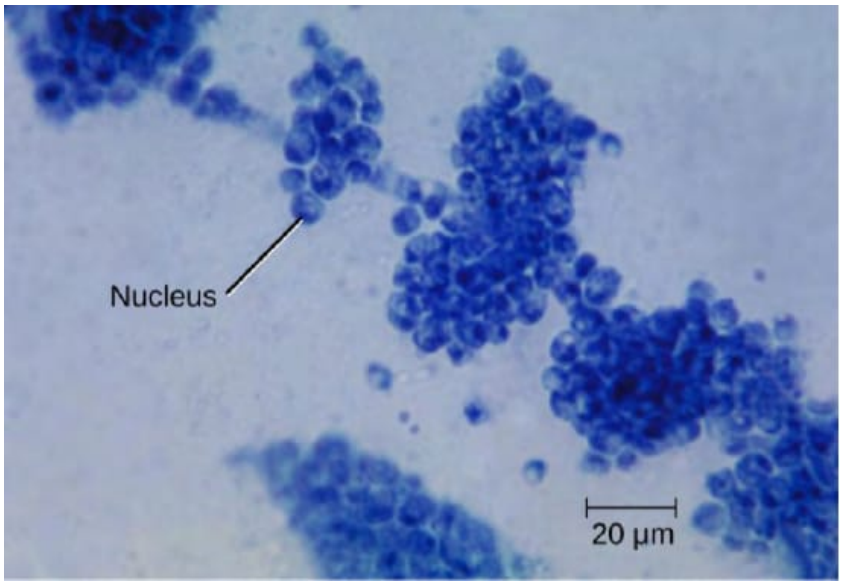



Figure 1.3.6: *Candida albicans* is a unicellular fungus, or yeast. It is the causative agent of vaginal yeast infections as well as oral thrush, a yeast infection of the mouth that commonly afflicts infants. *C. albicans* has a morphology similar to that of coccus bacteria; however, yeast is a eukaryotic organism (note the nuclei) and is much larger. (credit: modification of work by Centers for Disease Control and Prevention)

Other fungi of interest to microbiologists are multicellular organisms called molds. Molds are made up of long filaments that form visible colonies (***Figure*** 1.3.7). Molds are found in many different environments, from soil to rotting food to dank bathroom corners. Molds play a critical role in the decomposition of dead plants and animals. Some molds can cause allergies, and others produce disease-causing metabolites called mycotoxins. Molds have been used to make pharmaceuticals, including penicillin, which is one of the most commonly prescribed antibiotics, and cyclosporine, used to prevent organ rejection following a transplant.



Figure 1.3.7: Large colonies of microscopic fungi can often be observed with the naked eye, as seen on the surface of these moldy oranges.

## Exercise 1.3.2

- Name two types of protists and two types of fungi.
- Name some of the defining characteristics of each type.

# Helminths

Multicellular parasitic worms called **helminths** are not technically microorganisms, as most are large enough to see without a microscope. However, these worms fall within the field of microbiology because diseases caused by helminths involve microscopic eggs and larvae. One example of a helminth is the guinea worm, or Dracunculus medinensis, which causes dizziness, vomiting, diarrhea, and painful ulcers on the legs and feet when the worm works its way out of the skin (***Figure*** 1.3.8). Infection typically occurs after a person drinks water containing water fleas infected by guinea-worm larvae. In the mid-1980s, there were an estimated 3.5 million cases of guinea-worm disease, but the disease has been largely eradicated. In 2014, there were only 126 cases reported, thanks to the coordinated efforts of the World Health Organization (WHO) and other groups committed to improvements in drinking water sanitation.[1][2]

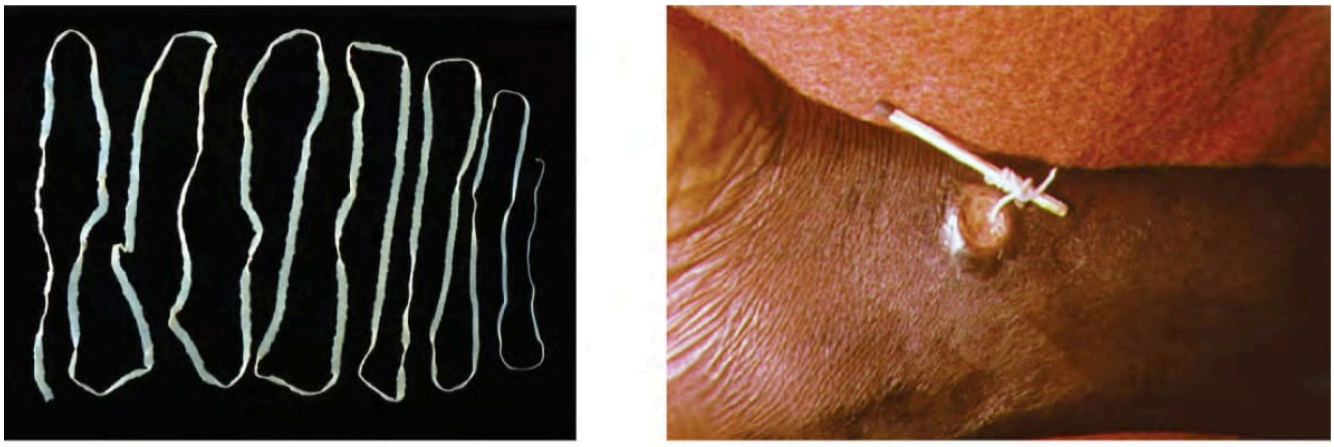



Figure 1.3.8: (a) The beef tapeworm, *Taenia saginata*, infects both cattle and humans. *T. saginata* eggs are microscopic (around 50 µm), but adult worms like the one shown here can reach 4–10 m, taking up residence in the digestive system. (b) An adult guinea worm, *Dracunculus medinensis*, is removed through a lesion in the patient's skin by winding it around a matchstick. (credit a, b: modification of work by Centers for Disease Control and Prevention)

# Viruses

**Viruses** are **acellular** microorganisms, which means they are not composed of cells. Essentially, a virus consists of proteins and genetic material—either DNA or RNA, but never both—that are inert outside of a host organism. However, by incorporating themselves into a host cell, viruses are able to co-opt the host's cellular mechanisms to multiply and infect other hosts.

Viruses can infect all types of cells, from human cells to the cells of other microorganisms. In humans, viruses are responsible for numerous diseases, from the common cold to deadly Ebola (***Figure*** 1.3.9). However, many viruses do not cause disease.

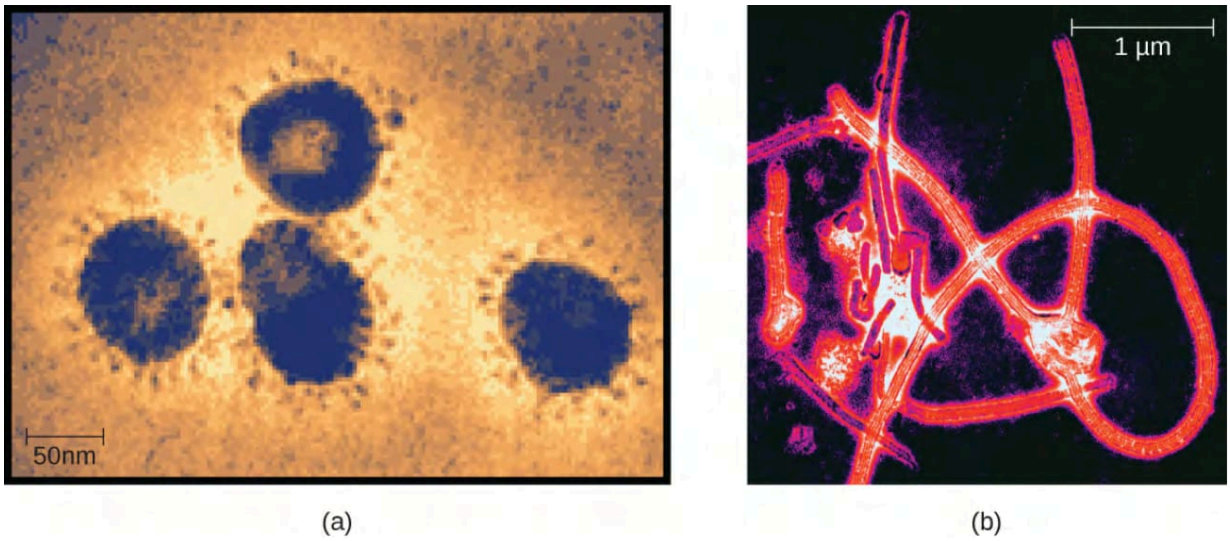



Figure 1.3.9: (a) Members of the Coronavirus family can cause respiratory infections like the common cold, severe acute respiratory syndrome (SARS), and Middle East respiratory syndrome (MERS). Here they are viewed under a transmission electron microscope (TEM). (b) Ebolavirus, a member of the Filovirus family, as visualized using a TEM. (credit a: modification of work by Centers for Disease Control and Prevention; credit b: modification of work by Thomas W. Geisbert)

**Exercise 1.3.3**

- Are helminths microorganisms? Explain why or why not.
- How are viruses different from other microorganisms?

## Microbiology as a Field of Study

**Microbiology** is a broad term that encompasses the study of all different types of microorganisms. But in practice, microbiologists tend to specialize in one of several subfields. For example, **bacteriology** is the study of bacteria; **mycology** is the study of fungi; **protozoology** is the study of protozoa; **parasitology** is the study of helminths and other parasites; and **virology** is the study of viruses (***Figure*** 1.3.10). **Immunology**, the study of the immune system, is often included in the study of microbiology because host–pathogen interactions are central to our understanding of infectious disease processes. Microbiologists can also specialize in certain areas of microbiology, such as clinical microbiology, environmental microbiology, applied microbiology, or food microbiology.

In this textbook, we are primarily concerned with clinical applications of microbiology, but since the various subfields of microbiology are highly interrelated, we will often discuss applications that are not strictly clinical.



Figure 1.3.10: A virologist samples eggs from this nest to be tested for the influenza A virus, which causes avian flu in birds. (credit: U.S. Fish and Wildlife Service)

## Eye on Ethics

**Bioethics in Microbiology**

In the 1940s, the U.S. government was looking for a solution to a medical problem: the prevalence of sexually transmitted diseases (STDs) among soldiers. Several now-infamous government-funded studies used human subjects to research common STDs and treatments. In one such study, American researchers intentionally exposed more than 1300 human subjects in Guatemala to syphilis, gonorrhea, and chancroid to determine the ability of penicillin and other antibiotics to combat these diseases. Subjects of the study included Guatemalan soldiers, prisoners, prostitutes, and psychiatric patients—none of whom were informed that they were taking part in the study. Researchers exposed subjects to STDs by various methods, from facilitating intercourse with infected prostitutes to inoculating subjects with the bacteria known to cause the diseases. This latter method involved making a small wound on the subject's genitals or elsewhere on the body, and then putting bacteria directly into the wound.[3] In 2011, a U.S. government commission tasked with investigating the experiment revealed that only some of the subjects were treated with penicillin, and 83 subjects died by 1953, likely as a result of the study.[4]

Unfortunately, this is one of many horrific examples of microbiology experiments that have violated basic ethical standards. Even if this study had led to a life-saving medical breakthrough (it did not), few would argue that its methods were ethically sound or morally justifiable. But not every case is so clear cut. Professionals working in clinical settings are frequently confronted with ethical dilemmas, such as working with patients who decline a vaccine or life-saving blood transfusion. These are just two examples of life-and-death decisions that may intersect with the religious and philosophical beliefs of both the patient and the health-care professional.

No matter how noble the goal, microbiology studies and clinical practice must be guided by a certain set of ethical principles. Studies must be done with integrity. Patients and research subjects provide informed consent (not only agreeing to be treated or studied but demonstrating an understanding of the purpose of the study and any risks involved). Patients' rights must be respected. Procedures must be approved by an institutional review board. When working with patients, accurate record-keeping, honest communication, and confidentiality are paramount. Animals used for research must be treated humanely, and all protocols must be approved by an institutional animal care and use committee. These are just a few of the ethical principles explored in the *Eye on Ethics* boxes throughout this book.

## Clinical Focus

**Resolution**

Cora's CSF samples show no signs of inflammation or infection, as would be expected with a viral infection. However, there is a high concentration of a particular protein, 14-3-3 protein, in her CSF. An electroencephalogram (EEG) of her brain function is also abnormal. The EEG resembles that of a patient with a neurodegenerative disease like Alzheimer's or Huntington's, but Cora's rapid cognitive decline is not consistent with either of these. Instead, her doctor concludes that Cora has Creutzfeldt-Jakob disease (CJD), a type of transmissible spongiform encephalopathy (TSE).

CJD is an extremely rare disease, with only about 300 cases in the United States each year. It is not caused by a bacterium, fungus, or virus, but rather by prions—which do not fit neatly into any particular category of microbe. Like viruses, prions are not found on the tree of life because they are acellular. Prions are extremely small, about one-tenth the size of a typical virus. They contain no genetic material and are composed solely of a type of abnormal protein.

CJD can have several different causes. It can be acquired through exposure to the brain or nervous- system tissue of an infected person or animal. Consuming meat from an infected animal is one way such exposure can occur. There have also been rare cases of exposure to CJD through contact with contaminated surgical equipment[5] and from cornea and growth-hormone donors who unknowingly had CJD.[6][7] In rare cases, the disease results from a specific genetic mutation that can sometimes be hereditary. However, in approximately 85% of patients with CJD, the cause of the disease is spontaneous (or sporadic) and has no identifiable cause.[8] Based on her symptoms and their rapid progression, Cora is diagnosed with sporadic CJD.

Unfortunately for Cora, CJD is a fatal disease for which there is no approved treatment. Approximately 90% of patients die within 1 year of diagnosis.[9] Her doctors focus on limiting her pain and cognitive symptoms as her disease progresses. Eight months later, Cora dies. Her CJD diagnosis is confirmed with a brain autopsy.

*Go back to the previous Clinical Focus box.*

## Key Concepts and Summary

- Microorganisms are very diverse and are found in all three domains of life: Archaea, Bacteria, and Eukarya.
- **Archaea** and **bacteria** are classified as prokaryotes because they lack a cellular nucleus. Archaea differ from
- bacteria in evolutionary history, genetics, metabolic pathways, and cell wall and membrane composition.
- Archaea inhabit nearly every environment on earth, but no archaea have been identified as human pathogens.
- **Eukaryotes** studied in microbiology include algae, protozoa, fungi, and helminths.
- **Algae** are plant-like organisms that can be either unicellular or multicellular, and derive energy via photosynthesis.
- **Protozoa** are unicellular organisms with complex cell structures; most are motile.
- Microscopic **fungi** include **molds** and **yeasts**.
- **Helminths** are multicellular parasitic worms. They are included in the field of microbiology because their eggs and larvae are often microscopic.
- **Viruses** are acellular microorganisms that require a host to reproduce.
- The field of microbiology is extremely broad. Microbiologists typically specialize in one of many subfields, but all health professionals need a solid foundation in clinical microbiology.

## Footnotes

1. C. Greenaway "Dracunculiasis (Guinea Worm Disease)." *Canadian Medical Association Journal* 170 no. 4 (2004):495–500.
2. World Health Organization. "Dracunculiasis (Guinea-Worm Disease)." WHO. 2015. http://www.who.int/mediacentre/factsheets/fs359/en/. Accessed October 2, 2015.
3. Kara Rogers. "Guatemala Syphilis Experiment: American Medical Research Project". *Encyclopedia Britannica*. http://www.britannica.com/event/Guat...lis-experiment. Accessed June 24, 2015.
4. Susan Donaldson James. "Syphilis Experiments Shock, But So Do Third-World Drug Trials." *ABC World News*. August 30, 2011. http://abcnews.go.com/Health/guatema...ry?id=14414902. Accessed June 24, 2015.
5. Greg Botelho. "Case of Creutzfeldt-Jakob Disease Confirmed in New Hampshire." *CNN*. 2013. http://www.cnn.com/2013/09/20/health/ creutzfeldt-jakob-brain-disease/.
6. P. Rudge et al. "Iatrogenic CJD Due to Pituitary-Derived Growth Hormone With Genetically Determined Incubation Times of Up to 40 Years." *Brain* 138 no. 11 (2015): 3386–3399.
7. J.G. Heckmann et al. "Transmission of Creutzfeldt-Jakob Disease via a Corneal Transplant." *Journal of Neurology, Neurosurgery & Psychiatry* 63 no. 3 (1997): 388–390.

8. National Institute of Neurological Disorders and Stroke. “Creutzfeldt-Jakob Disease Fact Sheet.” *NIH*. 2015. http://www.ninds.nih.gov/ disorders/cjd/detail_cjd.htm#288133058.
9. National Institute of Neurological Disorders and Stroke. “Creutzfeldt-Jakob Disease Fact Sheet.” *NIH*. 2015. http://www.ninds.nih.gov/ disorders/cjd/detail_cjd.htm#288133058. Accessed June 22, 2015.

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# 1.4: Review Questions

## Multiple Choice

1. Which of the following foods is NOT made by fermentation?
   A. beer
   B. bread
   C. cheese
   D. orange juice

*Answer available at the end of this section.*

2. Who is considered the “father of Western medicine”?
   A. Marcus Terentius Varro
   B. Thucydides
   C. Antonie van Leeuwenhoek
   D. Hippocrates

*Answer available at the end of this section.*

3. Who was the first to observe “animalcules” under the microscope?
   A. Antonie van Leeuwenhoek
   B. Ötzi the Iceman
   C. Marcus Terentius Varro
   D. Robert Koch

*Answer available at the end of this section.*

4. Who proposed that swamps might harbor tiny, disease-causing animals too small to see?
   A. Thucydides
   B. Marcus Terentius Varro
   C. Hippocrates
   D. Louis Pasteur

*Answer available at the end of this section.*

5. Which of the following was NOT a kingdom in Linnaeus’s taxonomy?
   A. animal
   B. mineral
   C. protist
   D. plant

*Answer available at the end of this section.*

6. Which of the following is a correct usage of binomial nomenclature?
   A. Homo Sapiens
   B. homo sapiens
   C. Homo sapiens
   D. Homo Sapiens

*Answer available at the end of this section.*

7. Which scientist proposed adding a kingdom for protists?
   A. Carolus Linnaeus
   B. Carl Woese

C. Robert Whittaker
D. Ernst Haeckel

*Answer available at the end of this section.*

8. Which of the following is NOT a domain in Woese and Fox's phylogenetic tree?
   A. Plantae
   B. Bacteria
   C. Archaea
   D. Eukarya

*Answer available at the end of this section.*

9. Which of the following is the standard resource for identifying bacteria?
   A. Systema Naturae
   B. Bergey's Manual of Determinative Bacteriology
   C. Woese and Fox's phylogenetic tree
   D. Haeckel's General Morphology of Organisms

*Answer available at the end of this section.*

10. Which of the following types of microorganisms is photosynthetic?
    A. yeast
    B. virus
    C. helminth
    D. alga

*Answer available at the end of this section.*

11. Which of the following is a prokaryotic microorganism?
    A. helminth
    B. protozoan
    C. cyanobacterium
    D. mold

*Answer available at the end of this section.*

12. Which of the following is acellular?
    A. virus
    B. bacterium
    C. fungus
    D. protozoan

*Answer available at the end of this section.*

13. Which of the following is a type of fungal microorganism?
    A. bacterium
    B. protozoan
    C. alga
    D. yeast

*Answer available at the end of this section.*

14. Which of the following is not a subfield of microbiology?
    A. bacteriology
    B. botany
    C. clinical microbiology
    D. virology

*Answer available at the end of this section.*

## Fill in the Blank

15. Thucydides is known as the father of _____.

    *Answer available at the end of this section.*

16. Researchers think that Ötzi the Iceman may have been infected with ____ disease.

    *Answer available at the end of this section.*

17. The process by which microbes turn grape juice into wine is called _____.

    *Answer available at the end of this section.*

18. In binomial nomenclature, an organism's scientific name includes its _____ and _____.

    *Answer available at the end of this section.*

19. Haeckel proposed adding the kingdoms _____ and _____ to his phylogenetic tree.

    *Answer available at the end of this section.*

20. _____ are organisms without membrane-bound nuclei.

    *Answer available at the end of this section.*

21. _____ are microorganisms that are not included in phylogenetic trees because they are acellular.

    *Answer available at the end of this section.*

22. A _____ is a disease-causing microorganism.

    *Answer available at the end of this section.*

23. Multicellular parasitic worms studied by microbiologists are called _____.

    *Answer available at the end of this section.*

24. The study of viruses is _____.

    *Answer available at the end of this section.*

25. The cells of prokaryotic organisms lack a _____.

    *Answer available at the end of this section.*

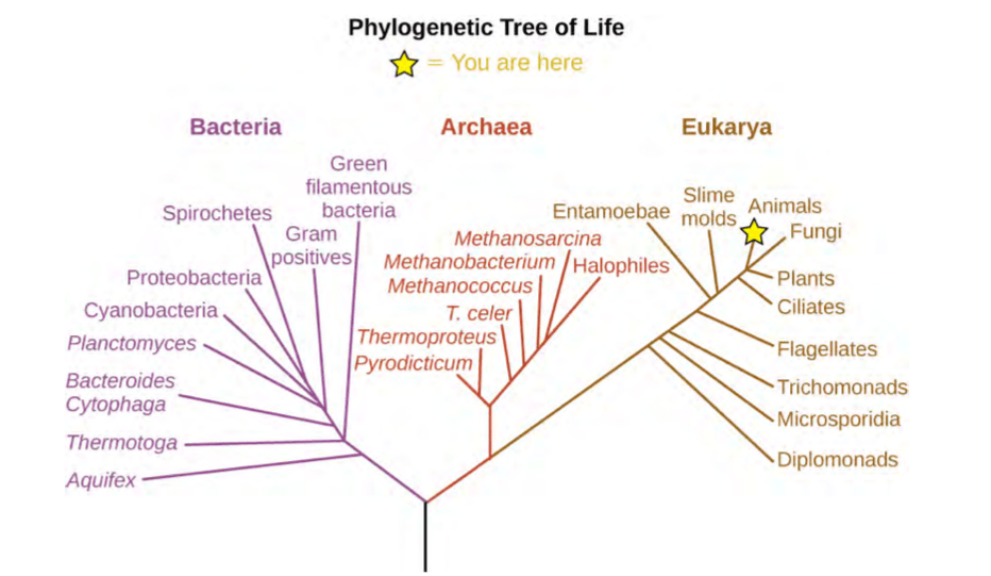
## Short Answer

26. What did Thucydides learn by observing the Athenian plague?
27. Why was the invention of the microscope important for microbiology?
28. What are some ways people use microbes?
29. What is a phylogenetic tree?

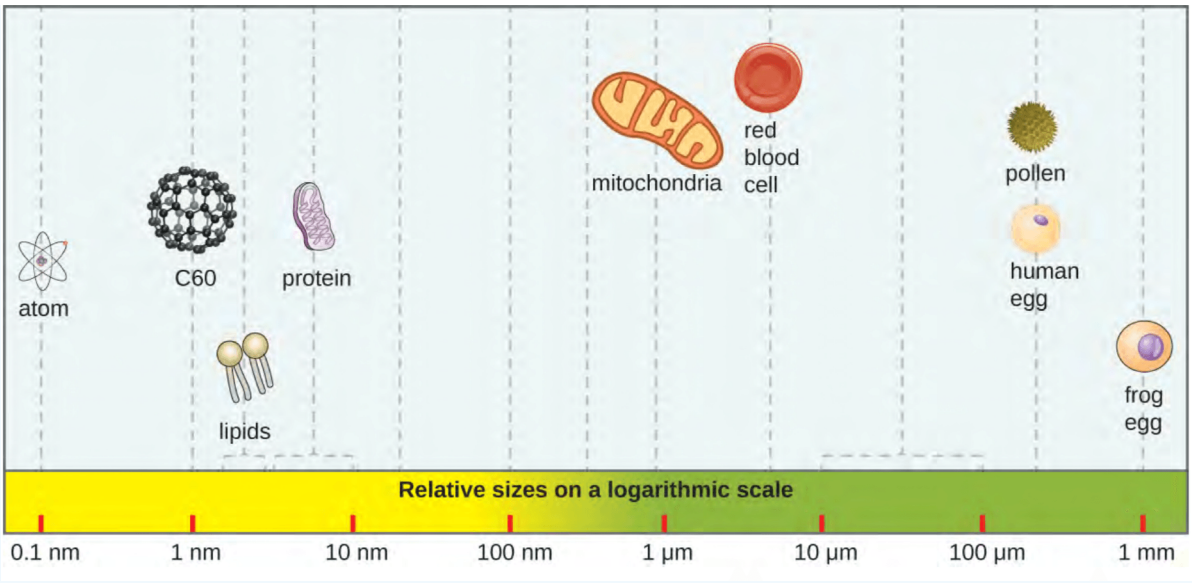
30. Which of the five kingdoms in Whittaker's phylogenetic tree are prokaryotic, and which are eukaryotic?
31. What molecule did Woese and Fox use to construct their phylogenetic tree?
32. Name some techniques that can be used to identify and differentiate species of bacteria.
33. Describe the differences between bacteria and archaea.
34. Name three structures that various protozoa use for locomotion.
35. Describe the actual and relative sizes of a virus, a bacterium, and a plant or animal cell.

## Critical Thinking

36. Explain how the discovery of fermented foods likely benefited our ancestors.
37. What evidence would you use to support this statement: Ancient people thought that disease was transmitted by things they could not see.
38. Why is using binomial nomenclature more useful than using common names?
39. Label the three Domains found on modern phylogenetic trees.




40. Contrast the behavior of a virus outside versus inside a cell.
41. Where would a virus, bacterium, animal cell, and a prion belong on this chart?




## Answers

**Multiple Choice**
D

**Multiple Choice**
D

**Multiple Choice**
A

**Multiple Choice**
B

**Multiple Choice**
C

**Multiple Choice**
C

**Multiple Choice**
D

**Multiple Choice**
A

**Multiple Choice**
B

**Multiple Choice**
D

**Multiple Choice**
C

**Multiple Choice**
A

**Multiple Choice**
D

**Multiple Choice**
B

**Fill in the Blank**
scientific history

**Fill in the Blank**
Lyme

**Fill in the Blank**
fermentation

**Fill in the Blank**
genus, species

**Fill in the Blank**
Protista and Monera

**Fill in the Blank**
Prokaryotes

**Fill in the Blank**
Viruses

**Fill in the Blank**
pathogen

**Fill in the Blank**
helminths

**Fill in the Blank**
virology

**Fill in the Blank**
nucleus

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# 1: AN INVISIBLE WORLD

From boiling thermal hot springs to deep beneath the Antarctic ice, microorganisms can be found almost everywhere on earth in great quantities. Microorganisms (or microbes, as they are also called) are small organisms. Most are so small that they cannot be seen without a microscope.

Most microorganisms are harmless to humans and, in fact, many are helpful. They play fundamental roles in ecosystems everywhere on earth, forming the backbone of many food webs. People use them to make biofuels, medicines, and even foods. Without microbes, there would be no bread, cheese, or beer. Our bodies are filled with microbes, and our skin alone is home to trillions of them.[1] Some of them we can't live without; others cause diseases that can make us sick or even kill us.

Although much more is known today about microbial life than ever before, the vast majority of this invisible world remains unexplored. Microbiologists continue to identify new ways that microbes benefit and threaten humans.

## Chapter Outline


1.1: What Our Ancestors Knew

1.2: Systematic Approach

1.3: Types of Microorganisms

1.4: Review Questions


## Footnotes

1. J. Hulcr et al. "A Jungle in There: Bacteria in Belly Buttons are Highly Diverse, but Predictable." PLoS ONE 7 no. 11 (2012): e47712. doi:10.1371/journal.pone.0047712.


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# WEEK 2

## 2: Disease and Epidemiology (Part A)

2.1: Tracking Infectious Diseases

2.2: Review Questions

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# 2.1: Tracking Infectious Diseases

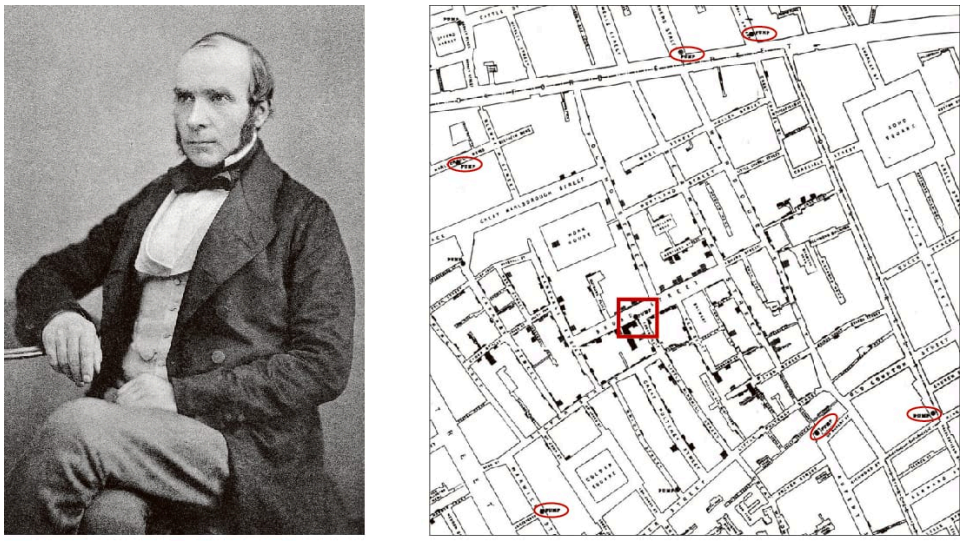
**Learning Objectives**

- Explain the research approaches used by the pioneers of epidemiology
- Explain how descriptive, analytical, and experimental epidemiological studies go about determining the cause of morbidity and mortality

Epidemiology has its roots in the work of physicians who looked for patterns in disease occurrence as a way to understand how to prevent it. The idea that disease could be transmitted was an important precursor to making sense of some of the patterns. In 1546, Girolamo Fracastoro first proposed the germ theory of disease in his essay *De Contagione et Contagiosis Morbis*, but this theory remained in competition with other theories, such as the miasma hypothesis, for many years (see What Our Ancestors Knew). Uncertainty about the cause of disease was not an absolute barrier to obtaining useful knowledge from patterns of disease. Some important researchers, such as Florence Nightingale, subscribed to the miasma hypothesis. The transition to acceptance of the germ theory during the 19th century provided a solid mechanistic grounding to the study of disease patterns. The studies of 19th century physicians and researchers such as John Snow, Florence Nightingale, Ignaz Semmelweis, Joseph Lister, Robert Koch, Louis Pasteur, and others sowed the seeds of modern epidemiology.

## Pioneers of Epidemiology

John Snow (Figure 2.1.1) was a British physician known as the father of epidemiology for determining the source of the 1854 Broad Street cholera epidemic in London. Based on observations he had made during an earlier cholera outbreak (1848–1849), Snow proposed that cholera was spread through a fecal-oral route of transmission and that a microbe was the infectious agent. He investigated the 1854 cholera epidemic in two ways. First, suspecting that contaminated water was the source of the epidemic, Snow identified the source of water for those infected. He found a high frequency of cholera cases among individuals who obtained their water from the River Thames downstream from London. This water contained the refuse and sewage from London and settlements upstream. He also noted that brewery workers did not contract cholera and on investigation found the owners provided the workers with beer to drink and stated that they likely did not drink water.[1] Second, he also painstakingly mapped the incidence of cholera and found a high frequency among those individuals using a particular water pump located on Broad Street. In response to Snow's advice, local officials removed the pump's handle,[2] resulting in the containment of the Broad Street cholera epidemic.



(a) (b)

Figure 2.1.1: (a) John Snow (1813–1858), British physician and father of epidemiology. (b) Snow's detailed mapping of cholera incidence led to the discovery of the contaminated water pump on Broad street (red square) responsible for the 1854 cholera epidemic. (credit a: modification of work by "Rsabbatini"/Wikimedia Commons)

Snow's work represents an early epidemiological study and it resulted in the first known public health response to an epidemic. Snow's meticulous case-tracking methods are now common practice in studying disease outbreaks and in associating new diseases with their causes. His work further shed light on unsanitary sewage practices and the effects of waste dumping in the Thames. Additionally, his work supported the germ theory of disease, which argued disease could be transmitted through contaminated items, including water contaminated with fecal matter.

Snow's work illustrated what is referred to today as a common source spread of infectious disease, in which there is a single source for all of the individuals infected. In this case, the single source was the contaminated well below the Broad Street pump. Types of common source spread include point source spread, continuous common source spread, and intermittent common source spread. In point source spread of infectious disease, the common source operates for a short time period—less than the incubation period of the pathogen. An example of point source spread is a single contaminated potato salad at a group picnic. In continuous common source spread, the infection occurs for an extended period of time, longer than the incubation period. An example of continuous common source spread would be the source of London water taken downstream of the city, which was continuously contaminated with sewage from upstream. Finally, with intermittent common source spread, infections occur for a period, stop, and then begin again. This might be seen in infections from a well that was contaminated only after large rainfalls and that cleared itself of contamination after a short period.

In contrast to common source spread, propagated spread occurs through direct or indirect person-to-person contact. With propagated spread, there is no single source for infection; each infected individual becomes a source for one or more subsequent infections. With propagated spread, unless the spread is stopped immediately, infections occur for longer than the incubation period. Although point sources often lead to large-scale but localized outbreaks of short duration, propagated spread typically results in longer duration outbreaks that can vary from small to large, depending on the population and the disease (Figure 2.1.2). In addition, because of person-to-person transmission, propagated spread cannot be easily stopped at a single source like point source spread.

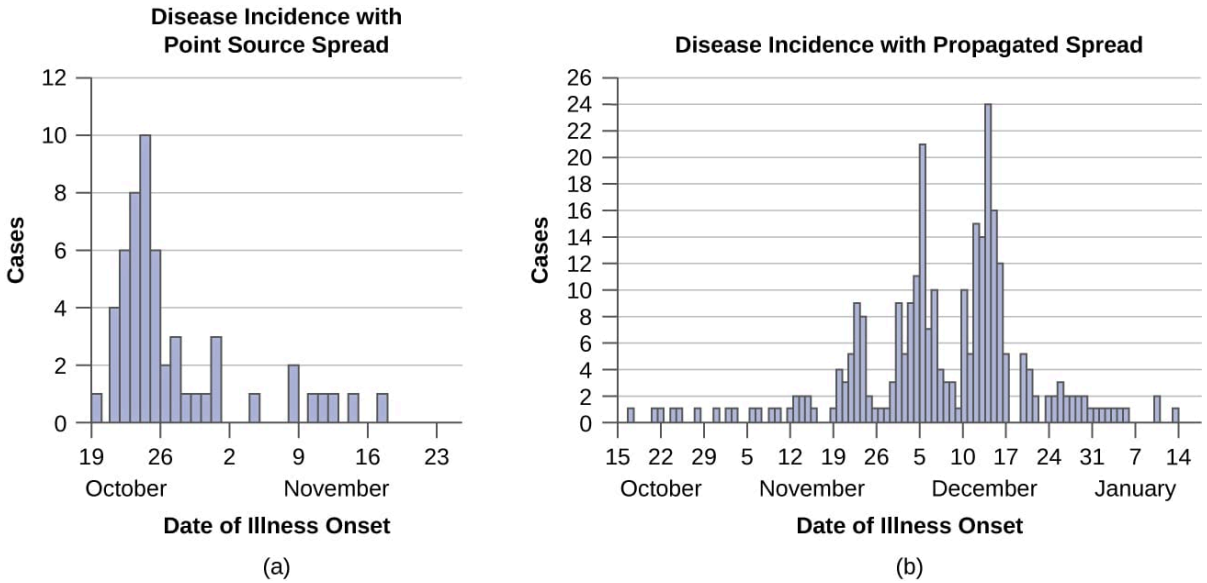


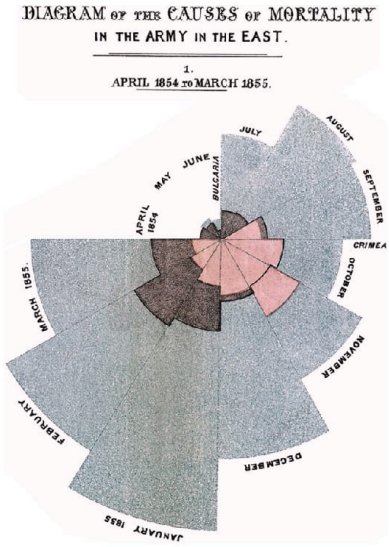

Figure 2.1.2: (a) Outbreaks that can be attributed to point source spread often have a short duration. (b) Outbreaks attributed to propagated spread can have a more extended duration. (credit a, b: modification of work by Centers for Disease Control and Prevention)

Florence Nightingale's work is another example of an early epidemiological study. In 1854, Nightingale was part of a contingent of nurses dispatched by the British military to care for wounded soldiers during the Crimean War. Nightingale kept meticulous records regarding the causes of illness and death during the war. Her recordkeeping was a fundamental task of what would later become the science of epidemiology. Her analysis of the data she collected was published in 1858. In this book, she presented monthly frequency data on causes of death in a wedge chart histogram (Figure 2.1.3). This graphical presentation of data, unusual at the time, powerfully illustrated that the vast majority of casualties during the war occurred not due to wounds sustained in action but to what Nightingale deemed preventable infectious diseases. Often these diseases occurred because of poor sanitation and lack of access to hospital facilities. Nightingale's findings led to many reforms in the British military's system of medical care.

Joseph Lister provided early epidemiological evidence leading to good public health practices in clinics and hospitals. These settings were notorious in the mid-1800s for fatal infections of surgical wounds at a time when the germ theory of disease was not yet widely accepted (see Foundations of Modern Cell Theory). Most physicians did not wash their hands between patient visits or clean and sterilize their surgical tools. Lister, however, discovered the disinfecting properties of carbolic acid, also known as phenol (see Using Chemicals to Control Microorganisms). He introduced several disinfection protocols that dramatically lowered post-surgical infection rates.[3] He demanded that surgeons who worked for him use a 5% carbolic acid solution to clean their surgical tools between patients, and even went so far as to spray the solution onto bandages and over the surgical site during operations (Figure 2.1.4). He also took precautions not to introduce sources of infection from his skin or clothing by removing his coat, rolling up his sleeves, and washing his hands in a dilute solution of carbolic acid before and during the surgery.



(a)




(b)

Figure 2.1.3: (a) Florence Nightingale reported on the data she collected as a nurse in the Crimean War. (b) Nightingale's diagram shows the number of fatalities in soldiers by month of the conflict from various causes. The total number dead in a particular month is equal to the area of the wedge for that month. The colored sections of the wedge represent different causes of death: wounds (pink), preventable infectious diseases (gray), and all other causes (brown).

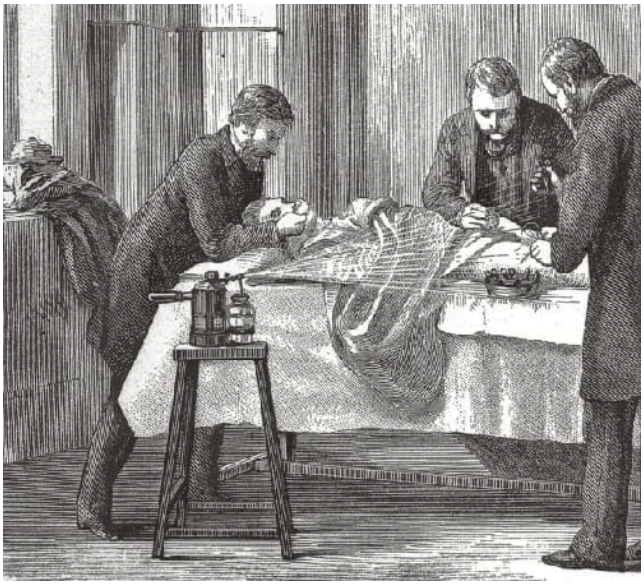


Figure 2.1.4: Joseph Lister initiated the use of a carbolic acid (phenol) during surgeries. This illustration of a surgery shows a pressurized canister of carbolic acid being sprayed over the surgical site.

## Link to Learning

John Snow's own account of his work has additional links and information.

This CDC resource further breaks down the pattern expected from a point-source outbreak.

Learn more about Nightingale's wedge chart here.

## Exercise 2.1.1

1. Explain the difference between common source spread and propagated spread of disease.

2. Describe how the observations of John Snow, Florence Nightingale, and Joseph Lister led to improvements in public health.

# Types of Epidemiological Studies

Today, epidemiologists make use of study designs, the manner in which data are gathered to test a hypothesis, similar to those of researchers studying other phenomena that occur in populations. These approaches can be divided into observational studies (in which subjects are not manipulated) and experimental studies (in which subjects are manipulated). Collectively, these studies give modern-day epidemiologists multiple tools for exploring the connections between infectious diseases and the populations of susceptible individuals they might infect.

## Observational Studies

In an observational study, data are gathered from study participants through measurements (such as physiological variables like white blood cell count), or answers to questions in interviews (such as recent travel or exercise frequency). The subjects in an observational study are typically chosen at random from a population of affected or unaffected individuals. However, the subjects in an observational study are in no way manipulated by the researcher. Observational studies are typically easier to carry out than experimental studies, and in certain situations they may be the only studies possible for ethical reasons.

Observational studies are only able to measure associations between disease occurrence and possible causative agents; they do not necessarily prove a causal relationship. For example, suppose a study finds an association between heavy coffee drinking and lower incidence of skin cancer. This might suggest that coffee prevents skin cancer, but there may be another unmeasured factor involved, such as the amount of sun exposure the participants receive. If it turns out that coffee drinkers work more in offices and spend less time outside in the sun than those who drink less coffee, then it may be possible that the lower rate of skin cancer is due to less sun exposure, not to coffee consumption. The observational study cannot distinguish between these two potential causes.

There are several useful approaches in observational studies. These include methods classified as descriptive epidemiology and analytical epidemiology. Descriptive epidemiology gathers information about a disease outbreak, the affected individuals, and how the disease has spread over time in an exploratory stage of study. This type of study will involve interviews with patients, their contacts, and their family members; examination of samples and medical records; and even histories of food and beverages consumed. Such a study might be conducted while the outbreak is still occurring. Descriptive studies might form the basis for developing a hypothesis of causation that could be tested by more rigorous observational and experimental studies.

Analytical epidemiology employs carefully selected groups of individuals in an attempt to more convincingly evaluate hypotheses about potential causes for a disease outbreak. The selection of cases is generally made at random, so the results are not biased because of some common characteristic of the study participants. Analytical studies may gather their data by going back in time (retrospective studies), or as events unfold forward in time (prospective studies).

Retrospective studies gather data from the past on present-day cases. Data can include things like the medical history, age, gender, or occupational history of the affected individuals. This type of study examines associations between factors chosen or available to the researcher and disease occurrence.

Prospective studies follow individuals and monitor their disease state during the course of the study. Data on the characteristics of the study subjects and their environments are gathered at the beginning and during the study so that subjects who become ill may be compared with those who do not. Again, the researchers can look for associations between the disease state and variables that were measured during the study to shed light on possible causes.

Analytical studies incorporate groups into their designs to assist in teasing out associations with disease. Approaches to group-based analytical studies include cohort studies, case-control studies, and cross-sectional studies. The cohort method examines groups of individuals (called cohorts) who share a particular characteristic. For example, a cohort might consist of individuals born in the same year and the same place; or it might consist of people who practice or avoid a particular behavior, e.g., smokers or nonsmokers. In a cohort study, cohorts can be followed prospectively or studied retrospectively. If only a single cohort is followed, then the affected individuals are compared with the unaffected individuals in the same group. Disease outcomes are recorded and analyzed to try to identify correlations between characteristics of individuals in the cohort and disease incidence. Cohort studies are a useful way to determine the causes of a condition without violating the ethical prohibition of exposing subjects to

a risk factor. Cohorts are typically identified and defined based on suspected risk factors to which individuals have already been exposed through their own choices or circumstances.

Case-control studies are typically retrospective and compare a group of individuals with a disease to a similar group of individuals without the disease. Case-control studies are far more efficient than cohort studies because researchers can deliberately select subjects who are already affected with the disease as opposed to waiting to see which subjects from a random sample will develop a disease.

A cross-sectional study analyzes randomly selected individuals in a population and compares individuals affected by a disease or condition to those unaffected at a single point in time. Subjects are compared to look for associations between certain measurable variables and the disease or condition. Cross-sectional studies are also used to determine the prevalence of a condition.

## Experimental Studies

Experimental epidemiology uses laboratory or clinical studies in which the investigator manipulates the study subjects to study the connections between diseases and potential causative agents or to assess treatments. Examples of treatments might be the administration of a drug, the inclusion or exclusion of different dietary items, physical exercise, or a particular surgical procedure. Animals or humans are used as test subjects. Because experimental studies involve manipulation of subjects, they are typically more difficult and sometimes impossible for ethical reasons.

Koch's postulates require experimental interventions to determine the causative agent for a disease. Unlike observational studies, experimental studies can provide strong evidence supporting cause because other factors are typically held constant when the researcher manipulates the subject. The outcomes for one group receiving the treatment are compared to outcomes for a group that does not receive the treatment but is treated the same in every other way. For example, one group might receive a regimen of a drug administered as a pill, while the untreated group receives a placebo (a pill that looks the same but has no active ingredient). Both groups are treated as similarly as possible except for the administration of the drug. Because other variables are held constant in both the treated and the untreated groups, the researcher is more certain that any change in the treated group is a result of the specific manipulation.

Experimental studies provide the strongest evidence for the etiology of disease, but they must also be designed carefully to eliminate subtle effects of bias. Typically, experimental studies with humans are conducted as double-blind studies, meaning neither the subjects nor the researchers know who is a treatment case and who is not. This design removes a well-known cause of bias in research called the placebo effect, in which knowledge of the treatment by either the subject or the researcher can influence the outcomes.

### Exercise 2.1.2

1. Describe the advantages and disadvantages of observational studies and experimental studies.
2. Explain the ways that groups of subjects can be selected for analytical studies.

### Clinical Focus

**Part 3**

Since laboratory tests had confirmed *Salmonella*, a common foodborne pathogen, as the etiologic agent, epidemiologists suspected that the outbreak was caused by contamination at a food processing facility serving the region. Interviews with patients focused on food consumption during and after the Thanksgiving holiday, corresponding with the timing of the outbreak. During the interviews, patients were asked to list items consumed at holiday gatherings and describe how widely each item was consumed among family members and relatives. They were also asked about the sources of food items (e.g., brand, location of purchase, date of purchase). By asking such questions, health officials hoped to identify patterns that would lead back to the source of the outbreak.

Analysis of the interview responses eventually linked almost all of the cases to consumption of a holiday dish known as the turducken—a chicken stuffed inside a duck stuffed inside a turkey. Turducken is a dish not generally consumed year-round, which would explain the spike in cases just after the Thanksgiving holiday. Additional analysis revealed that the turduckens consumed by the affected patients were purchased already stuffed and ready to be cooked. Moreover, the pre-stuffed turduckens were all sold at the same regional grocery chain under two different brand names. Upon further investigation, officials traced both brands to a single processing plant that supplied stores throughout the Florida panhandle.

- Is this an example of common source spread or propagated spread?
- What next steps would the public health office likely take after identifying the source of the outbreak?

Jump to the next Clinical Focus box. Go back to the previous Clinical Focus box.

## Key Concepts and Summary

- Early pioneers of epidemiology such as John Snow, Florence Nightingale, and Joseph Lister, studied disease at the population level and used data to disrupt disease transmission.
- **Descriptive epidemiology** studies rely on case analysis and patient histories to gain information about outbreaks, frequently while they are still occurring.
- **Retrospective epidemiology** studies use historical data to identify associations with the disease state of present cases. **Prospective epidemiology** studies gather data and follow cases to find associations with future disease states.
- **Analytical epidemiology** studies are observational studies that are carefully designed to compare groups and uncover associations between environmental or genetic factors and disease.
- **Experimental epidemiology** studies generate strong evidence of causation in disease or treatment by manipulating subjects and comparing them with control subjects.

## Footnotes

1. John Snow. *On the Mode of Communication of Cholera. Second edition, Much Enlarged*. John Churchill, 1855.
2. John Snow. “The Cholera near Golden-Wquare, and at Deptford.” *Medical Times and Gazette* 9 (1854): 321–322. http://www.ph.ucla.edu/epi/snow/chol...densquare.html.
3. O.M. Lidwell. “Joseph Lister and Infection from the Air.” *Epidemiology and Infection* 99 (1987): 569–578. www.ncbi.nlm.nih.gov/pmc/arti...00006-0004.pdf.

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# 2.2: Review Questions

## Matching

1. Match each type of epidemiology study with its description.

| | |
|---|---|
| ___experimental | A. examination of past case histories and medical test results conducted on patients in an outbreak |
| ___analytical | B. examination of current case histories, interviews with patients and their contacts, interpretation of medical test results; frequently conducted while outbreak is still in progress |
| ___prospective | C. use of a set of test subjects (human or animal) and control subjects that are treated the same as the test subjects except for the specific treatment being studied |
| ___descriptive | D. observing groups of individuals to look for associations with disease |
| ___retrospective | E. a comparison of a cohort of individuals through the course of the study |

*Answer available at the end of this section.*

2. Match each pioneer of epidemiology with his or her contribution.

| | |
|---|---|
| ___Florence Nightingale | A. determined the source of a cholera outbreak in London |
| ___Robert Koch | B. showed that surgical wound infection rates could be dramatically reduced by using carbolic acid to disinfect surgical tools, bandages, and surgical sites |
| ___Joseph Lister | C. compiled data on causes of mortality in soldiers, leading to innovations in military medical care |
| ___John Snow | D. developed a methodology for conclusively determining the etiology of disease |

*Answer available at the end of this section.*

## Fill in the Blank

3. _____occurs when an infected individual passes the infection on to other individuals, who pass it on to still others, increasing the penetration of the infection into the susceptible population.

*Answer available at the end of this section.*

4. A batch of food contaminated with botulism exotoxin, consumed at a family reunion by most of the members of a family, would be an example of a _____ outbreak.

*Answer available at the end of this section.*

## Short Answer

5. What activity did John Snow conduct, other than mapping, that contemporary epidemiologists also use when trying to understand how to control a disease?

## Answers

**Matching**

C, D, E, B, A

**Matching**

C, D, B, A

**Fill in the Blank**

Propagated spread

**Fill in the Blank**

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# 2: DISEASE AND EPIDEMIOLOGY (PART A)

In the United States and other developed nations, public health is a key function of government. A healthy citizenry is more productive, content, and prosperous; high rates of death and disease, on the other hand, can severely hamper economic productivity and foster social and political instability. The burden of disease makes it difficult for citizens to work consistently, maintain employment, and accumulate wealth to better their lives and support a growing economy.

In this chapter, we will explore the intersections between microbiology and epidemiology, the science that underlies public health.

## Chapter Outline

2.1: Tracking Infectious Diseases

2.2: Review Questions

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# WEEK 3

## 3: Microbial Mechanisms of Pathogenicity


3.1: Characteristics of Infectious Disease

3.2: How Pathogens Cause Disease

3.3: Virulence Factors of Bacterial and Viral Pathogens

3.4: Virulence Factors of Eukaryotic Pathogens

3.5: Review Questions


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# 3.1: Characteristics of Infectious Disease

**Learning Objectives**

- Distinguish between signs and symptoms of disease
- Explain the difference between a communicable disease and a noncommunicable disease
- Compare different types of infectious diseases, including iatrogenic, nosocomial, and zoonotic diseases
- Identify and describe the stages of an acute infectious disease in terms of number of pathogens present and severity of signs and symptoms

A **disease** is any condition in which the normal structure or functions of the body are damaged or impaired. Physical injuries or disabilities are not classified as disease, but there can be several causes for disease, including infection by a pathogen, genetics (as in many cancers or deficiencies), noninfectious environmental causes, or inappropriate immune responses. Our focus in this chapter will be on infectious diseases, although when diagnosing infectious diseases, it is always important to consider possible noninfectious causes.

## Signs and Symptoms of Disease

An **infection** is the successful colonization of a host by a microorganism. Infections can lead to disease, which causes signs and symptoms resulting in a deviation from the normal structure or functioning of the host. Microorganisms that can cause disease are known as pathogens.

The **signs** of disease are objective and measurable, and can be directly observed by a clinician. Vital signs, which are used to measure the body's basic functions, include body temperature (normally 37 °C [98.6 °F]), heart rate (normally 60–100 beats per minute), breathing rate (normally 12–18 breaths per minute), and blood pressure (normally between 90/60 and 120/80 mm Hg). Changes in any of the body's vital signs may be indicative of disease. For example, having a fever (a body temperature significantly higher than 37 °C or 98.6 °F) is a sign of disease because it can be measured.

In addition to changes in vital signs, other observable conditions may be considered signs of disease. For example, the presence of antibodies in a patient's serum (the liquid portion of blood that lacks clotting factors) can be observed and measured through blood tests and, therefore, can be considered a sign. However, it is important to note that the presence of antibodies is not always a sign of an active disease. Antibodies can remain in the body long after an infection has resolved; also, they may develop in response to a pathogen that is in the body but not currently causing disease.

**Clinical Focus**

**Part 1**

Michael, a 10-year-old boy in generally good health, went to a birthday party on Sunday with his family. He ate many different foods but was the only one in the family to eat the undercooked hot dogs served by the hosts. Monday morning, he woke up feeling achy and nauseous, and he was running a fever of 38 °C (100.4 °F). His parents, assuming Michael had caught the flu, made him stay home from school and limited his activities. But after 4 days, Michael began to experience severe headaches, and his fever spiked to 40 °C (104 °F). Growing worried, his parents finally decide to take Michael to a nearby clinic.

- What signs and symptoms is Michael experiencing?
- What do these signs and symptoms tell us about the stage of Michael's disease?

*Jump to the next Clinical Focus box.*

Unlike signs, **symptoms** of disease are subjective. Symptoms are felt or experienced by the patient, but they cannot be clinically confirmed or objectively measured. Examples of symptoms include nausea, loss of appetite, and pain. Such symptoms are important to consider when diagnosing disease, but they are subject to memory bias and are difficult to measure precisely. Some

clinicians attempt to quantify symptoms by asking patients to assign a numerical value to their symptoms. For example, the Wong-Baker Faces pain-rating scale asks patients to rate their pain on a scale of 0–10. An alternative method of quantifying pain is measuring skin conductance fluctuations. These fluctuations reflect sweating due to skin sympathetic nerve activity resulting from the stressor of pain.[1] A specific group of signs and symptoms characteristic of a particular disease is called a **syndrome**. Many syndromes are named using a nomenclature based on signs and symptoms or the location of the disease. ***Table*** 3.1.1 lists some of the prefixes and suffixes commonly used in naming syndromes.

*Table* 3.1.1*: Nomenclature of Symptoms*

| Affix | Meaning | Example |
|---|---|---|
| cyto- | cell | cytopenia: reduction in the number of blood cells |
| hepat- | of the liver | hepatitis: inflammation of the liver |
| -pathy | disease | neuropathy: a disease affecting nerves |
| -emia | of the blood | bacteremia: presence of bacteria in blood |
| -itis | inflammation | colitis: inflammation of the colon |
| -lysis | destruction | hemolysis: destruction of red blood cells |
| -oma | tumor | lymphoma: cancer of the lymphatic system |
| -osis | diseased or abnormal condition | leukocytosis: abnormally high number of white blood cells |
| -derma | of the skin | keratoderma: a thickening of the skin |

Clinicians must rely on signs and on asking questions about symptoms, medical history, and the patient's recent activities to identify a particular disease and the potential causative agent. Diagnosis is complicated by the fact that different microorganisms can cause similar signs and symptoms in a patient. For example, an individual presenting with symptoms of diarrhea may have been infected by one of a wide variety of pathogenic microorganisms. Bacterial pathogens associated with diarrheal disease include Vibrio cholerae, Listeria monocytogenes, Campylobacter jejuni, and enteropathogenic *Escherichia coli* (EPEC). Viral pathogens associated with diarrheal disease include norovirus and rotavirus. Parasitic pathogens associated with diarrhea include *Giardia lamblia* and *Cryptosporidium parvum*. Likewise, fever is indicative of many types of infection, from the common cold to the deadly Ebola hemorrhagic fever.

Finally, some diseases may be **asymptomatic** or **subclinical**, meaning they do not present any noticeable signs or symptoms. For example, most individual infected with herpes simplex virus remain asymptomatic and are unaware that they have been infected.

**Exercise 3.1.1**

- Explain the difference between signs and symptoms.

## Classifications of Disease

The World Health Organization's (WHO) International Classification of Diseases (ICD) is used in clinical fields to classify diseases and monitor morbidity (the number of cases of a disease) and mortality (the number of deaths due to a disease). In this section, we will introduce terminology used by the ICD (and in health-care professions in general) to describe and categorize various types of disease.

An infectious disease is any disease caused by the direct effect of a pathogen. A pathogen may be cellular (bacteria, parasites, and fungi) or acellular (viruses, viroids, and prions). Some infectious diseases are also communicable, meaning they are capable of being spread from person to person through either direct or indirect mechanisms. Some infectious communicable diseases are also considered contagious diseases, meaning they are easily spread from person to person. Not all contagious diseases are equally so; the degree to which a disease is contagious usually depends on how the pathogen is transmitted. For example, measles is a highly contagious viral disease that can be transmitted when an infected person coughs or sneezes and an uninfected person breathes in droplets containing the virus. Gonorrhea is not as contagious as measles because transmission of the pathogen (Neisseria gonorrhoeae) requires close intimate contact (usually sexual) between an infected person and an uninfected person.

Diseases that are contracted as the result of a medical procedure are known as iatrogenic diseases. Iatrogenic diseases can occur after procedures involving wound treatments, catheterization, or surgery if the wound or surgical site becomes contaminated. For example, an individual treated for a skin wound might acquire necrotizing fasciitis (an aggressive, "flesh-eating" disease) if bandages or other dressings became contaminated by Clostridium perfringensor one of several other bacteria that can cause this condition.

Diseases acquired in hospital settings are known as nosocomial diseases. Several factors contribute to the prevalence and severity of nosocomial diseases. First, sick patients bring numerous pathogens into hospitals, and some of these pathogens can be transmitted easily via improperly sterilized medical equipment, bed sheets, call buttons, door handles, or by clinicians, nurses, or therapists who do not wash their hands before touching a patient. Second, many hospital patients have weakened immune systems, making them more susceptible to infections. Compounding this, the prevalence of antibiotics in hospital settings can select for drug-resistant bacteria that can cause very serious infections that are difficult to treat.

Certain infectious diseases are not transmitted between humans directly but can be transmitted from animals to humans. Such a disease is called zoonotic disease (or zoonosis). According to WHO, a zoonosis is a disease that occurs when a pathogen is transferred from a vertebrate animal to a human; however, sometimes the term is defined more broadly to include diseases transmitted by all animals (including invertebrates). For example, rabies is a viral zoonotic disease spread from animals to humans through bites and contact with infected saliva. Many other zoonotic diseases rely on insects or other arthropods for transmission. Examples include yellow fever (transmitted through the bite of mosquitoes infected with yellow fever virus) and Rocky Mountain spotted fever (transmitted through the bite of ticks infected with Rickettsia rickettsii).

In contrast to communicable infectious diseases, a noncommunicable infectious disease is not spread from one person to another. One example is tetanus, caused by Clostridium tetani, a bacterium that produces endospores that can survive in the soil for many years. This disease is typically only transmitted through contact with a skin wound; it cannot be passed from an infected person to another person. Similarly, Legionnaires disease is caused by Legionella pneumophila, a bacterium that lives within amoebae in moist locations like water-cooling towers. An individual may contract Legionnaires disease via contact with the contaminated water, but once infected, the individual cannot pass the pathogen to other individuals.

In addition to the wide variety of noncommunicable infectious diseases, noninfectious diseases (those not caused by pathogens) are an important cause of morbidity and mortality worldwide. Noninfectious diseases can be caused by a wide variety factors, including genetics, the environment, or immune system dysfunction, to name a few. For example, sickle cell anemia is an inherited disease caused by a genetic mutation that can be passed from parent to offspring (***Figure*** 3.1.1). Other types of noninfectious diseases are listed in ***Table*** 3.1.2.

*Table* 3.1.2*: Types of Noninfectious Diseases*

| Type | Definition | Example |
|---|---|---|
| Inherited | A genetic disease | Sickle cell anemia |
| Congenital | Disease that is present at or before birth | Down syndrome |
| Degenerative | Progressive, irreversible loss of function | Parkinson disease (affecting central nervous system) |
| Nutritional deficiency | Impaired body function due to lack of nutrients | Scurvy (vitamin C deficiency) |
| Endocrine | Disease involving malfunction of glands that release hormones to regulate body functions | Hypothyroidism – thyroid does not produce enough thyroid hormone, which is important for metabolism |
| Neoplastic | Abnormal growth (benign or malignant) | Some forms of cancer |
| Idiopathic | Disease for which the cause is unknown | Idiopathic juxtafoveal retinal telangiectasia (dilated, twisted blood vessels in the retina of the eye) |

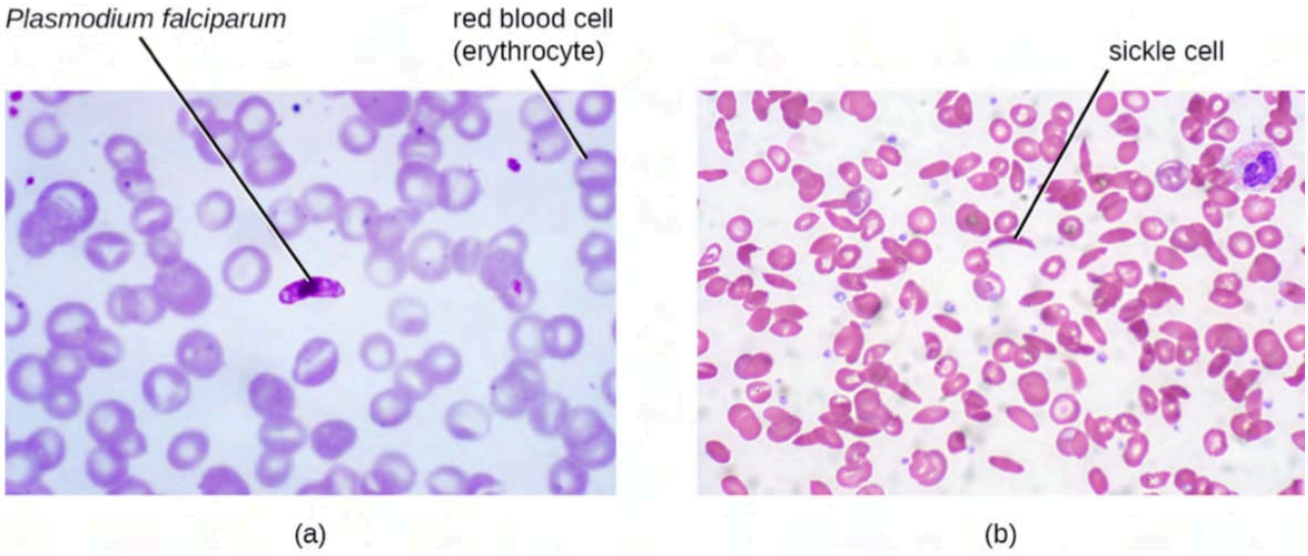



Figure 3.1.1: Blood smears showing two diseases of the blood. (a) Malaria is an infectious, zoonotic disease caused by the protozoan pathogen *Plasmodium falciparum* (shown here) and several other species of the genus *Plasmodium*. It is transmitted by mosquitoes to humans. (b) Sickle cell disease is a noninfectious genetic disorder that results in abnormally shaped red blood cells, which can stick together and obstruct the flow of blood through the circulatory system. It is not caused by a pathogen, but rather a genetic mutation. (credit a: modification of work by Centers for Disease Control and Prevention; credit b: modification of work by Ed Uthman)

**Link to Learning**

Lists of common infectious diseases can be found at the following Centers for Disease Control and Prevention (CDC), World Health Organization (WHO), and International Classification of Diseases websites.

**Exercise 3.1.2**

- Describe how a disease can be infectious but not contagious.
- Explain the difference between iatrogenic disease and nosocomial disease.

## Periods of Disease

The five periods of disease (sometimes referred to as stages or phases) include the incubation, prodromal, illness, decline, and convalescence periods (***Figure*** 3.1.2). The **incubation period** occurs in an acute disease after the initial entry of the pathogen into the host (patient). It is during this time the pathogen begins multiplying in the host. However, there are insufficient numbers of pathogen particles (cells or viruses) present to cause signs and symptoms of disease. Incubation periods can vary from a day or two in acute disease to months or years in chronic disease, depending upon the pathogen. Factors involved in determining the length of the incubation period are diverse, and can include strength of the pathogen, strength of the host immune defenses, site of infection, type of infection, and the size infectious dose received. During this incubation period, the patient is unaware that a disease is beginning to develop.

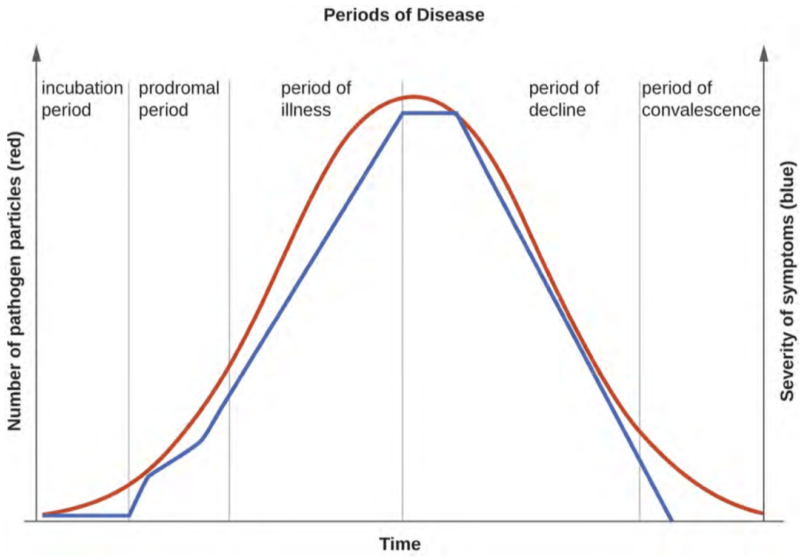



Figure 3.1.2: The progression of an infectious disease can be divided into five periods, which are related to the number of pathogen particles (red) and the severity of signs and symptoms (blue).

The **prodromal period** occurs after the incubation period. During this phase, the pathogen continues to multiply and the host begins to experience general signs and symptoms of illness, which typically result from activation of the immune system, such as fever, pain, soreness, swelling, or inflammation. Usually, such signs and symptoms are too general to indicate a particular disease. Following the prodromal period is the **period of illness**, during which the signs and symptoms of disease are most obvious and severe.

The period of illness is followed by the **period of decline**, during which the number of pathogen particles begins to decrease, and the signs and symptoms of illness begin to decline. However, during the decline period, patients may become susceptible to developing secondary infections because their immune systems have been weakened by the primary infection. The final period is known as the **period of convalescence**. During this stage, the patient generally returns to normal functions, although some diseases may inflict permanent damage that the body cannot fully repair.

Infectious diseases can be contagious during all five of the periods of disease. Which periods of disease are more likely to associated with transmissibility of an infection depends upon the disease, the pathogen, and the mechanisms by which the disease develops and progresses. For example, with meningitis (infection of the lining of brain), the periods of infectivity depend on the type of pathogen causing the infection. Patients with bacterial meningitis are contagious during the incubation period for up to a week before the onset of the prodromal period, whereas patients with viral meningitis become contagious when the first signs and symptoms of the prodromal period appear. With many viral diseases associated with rashes (e.g., chickenpox, measles, rubella, roseola), patients are contagious during the incubation period up to a week before the rash develops. In contrast, with many respiratory infections (e.g., colds, influenza, diphtheria, strep throat, and pertussis) the patient becomes contagious with the onset of the prodromal period. Depending upon the pathogen, the disease, and the individual infected, transmission can still occur during the periods of decline, convalescence, and even long after signs and symptoms of the disease disappear. For example, an individual recovering from a diarrheal disease may continue to carry and shed the pathogen in feces for some time, posing a risk of transmission to others through direct contact or indirect contact (e.g., through contaminated objects or food).

### Exercise 3.1.3

- Name some of the factors that can affect the length of the incubation period of a particular disease

## Acute and Chronic Diseases

The duration of the period of illness can vary greatly, depending on the pathogen, effectiveness of the immune response in the host, and any medical treatment received. For an acute disease, pathologic changes occur over a relatively short time (e.g., hours, days, or a few weeks) and involve a rapid onset of disease conditions. For example, influenza (caused by Influenzavirus) is

considered an acute disease because the incubation period is approximately 1–2 days. Infected individuals can spread influenza to others for approximately 5 days after becoming ill. After approximately 1 week, individuals enter the period of decline.

For a **chronic disease**, pathologic changes can occur over longer time spans (e.g., months, years, or a lifetime). For example, chronic gastritis (inflammation of the lining of the stomach) is caused by the gram-negative bacterium *Helicobacter pylori*. H. pylori is able to colonize the stomach and persist in its highly acidic environment by producing the enzyme urease, which modifies the local acidity, allowing the bacteria to survive indefinitely.[2] Consequently, H. pylori infections can recur indefinitely unless the infection is cleared using antibiotics.[3] Hepatitis B virus can cause a chronic infection in some patients who do not eliminate the virus after the acute illness. A chronic infection with hepatitis B virus is characterized by the continued production of infectious virus for 6 months or longer after the acute infection, as measured by the presence of viral antigen in blood samples.

In **latent diseases**, as opposed to chronic infections, the causal pathogen goes dormant for extended periods of time with no active replication. Examples of diseases that go into a latent state after the acute infection include herpes (herpes simplex viruses [HSV-1 and HSV-2]), chickenpox (varicella-zoster virus [VZV]), and mononucleosis (Epstein-Barr virus [EBV]). HSV-1, HSV-2, and VZV evade the host immune system by residing in a latent form within cells of the nervous system for long periods of time, but they can reactivate to become active infections during times of stress and immunosuppression. For example, an initial infection by VZV may result in a case of childhood chickenpox, followed by a long period of latency. The virus may reactivate decades later, causing episodes of shingles in adulthood. EBV goes into latency in B cells of the immune system and possibly epithelial cells; it can reactivate years later to produce B-cell lymphoma.

**Exercise 3.1.4**

- Explain the difference between latent disease and chronic disease

## Key Concepts and Summary

- In an **infection**, a microorganism enters a host and begins to multiply. Some infections cause **disease**, which is any deviation from the normal function or structure of the host.
- **Signs** of a disease are objective and are measured. **Symptoms** of a disease are subjective and are reported by the patient.
- Diseases can either be **noninfectious** (due to genetics and environment) or infectious (due to pathogens). Some infectious diseases are **communicable** (transmissible between individuals) or contagious (easily transmissible between individuals); others are **noncommunicable**, but may be contracted via contact with environmental reservoirs or animals (**zoonoses**)
- **Nosocomial diseases** are contracted in hospital settings, whereas **iatrogenic disease** are the direct result of a medical procedure
- An acute disease is short in duration, whereas a **chronic disease** lasts for months or years. **Latent diseases** last for years, but are distinguished from chronic diseases by the lack of active replication during extended dormant periods.
- The periods of disease include the **incubation period**, the **prodromal period**, the **period of illness**, the **period of decline**, and the **period of convalescence**. These periods are marked by changes in the number of infectious agents and the severity of signs and symptoms.

## Footnotes

1. F. Savino et al. “Pain Assessment in Children Undergoing Venipuncture: The Wong–Baker Faces Scale Versus Skin Conductance Fluctuations.” *PeerJ* 1 (2013):e37; https://peerj.com/articles/37/

2. J.G. Kusters et al. Pathogenesis of *Helicobacter pylori* Infection. *Clinical Microbiology Reviews* 19 no. 3 (2006):449–490.

3. N.R. Salama et al. “Life in the Human Stomach: Persistence Strategies of the Bacterial Pathogen *Helicobacter pylori*.” Nature Reviews *Microbiology* 11 (2013):385–399.

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# 3.2: How Pathogens Cause Disease

**Learning Objectives**

- Summarize Koch's postulates and molecular Koch's postulates, respectively, and explain their significance and limitations
- Explain the concept of pathogenicity (virulence) in terms of infectious and lethal dose
- Distinguish between primary and opportunistic pathogens and identify specific examples of each
- Summarize the stages of pathogenesis
- Explain the roles of portals of entry and exit in the transmission of disease and identify specific examples of these portals

For most infectious diseases, the ability to accurately identify the causative pathogen is a critical step in finding or prescribing effective treatments. Today's physicians, patients, and researchers owe a sizable debt to the physician Robert Koch (1843–1910), who devised a systematic approach for confirming causative relationships between diseases and specific pathogens.

## Koch's Postulates

In 1884, Koch published four postulates (***Table*** 3.2.1) that summarized his method for determining whether a particular microorganism was the cause of a particular disease. Each of Koch's postulates represents a criterion that must be met before a disease can be positively linked with a pathogen. In order to determine whether the criteria are met, tests are performed on laboratory animals and cultures from healthy and diseased animals are compared (***Figure*** 3.2.1 ).

*Table* 3.2.1*: Koch's Postulates*

| |
|---|
| (1) The suspected pathogen must be found in every case of disease and not be found in healthy individuals. |
| (2) The suspected pathogen can be isolated and grown in pure culture. |
| (3) A healthy test subject infected with the suspected pathogen must develop the same signs and symptoms of disease as seen in postulate 1. |
| (4) The pathogen must be re-isolated from the new host and must be identical to the pathogen from postulate 2. |

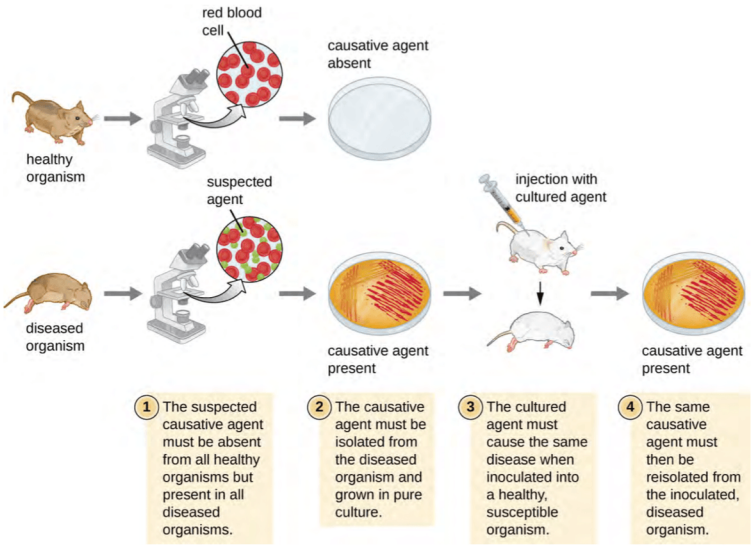



Figure 3.2.1: The steps for confirming that a pathogen is the cause of a particular disease using Koch's postulates.

In many ways, Koch's postulates are still central to our current understanding of the causes of disease. However, advances in microbiology have revealed some important limitations in Koch's criteria. Koch made several assumptions that we now know are untrue in many cases. The first relates to postulate 1, which assumes that pathogens are only found in diseased, not healthy, individuals. This is not true for many pathogens. For example, *H. pylori*, described earlier in this chapter as a pathogen causing chronic gastritis, is also part of the normal microbiota of the stomach in many healthy humans who never develop gastritis. It is estimated that upwards of 50% of the human population acquires *H. pylori* early in life, with most maintaining it as part of the normal microbiota for the rest of their life without ever developing disease.

Koch's second faulty assumption was that all healthy test subjects are equally susceptible to disease. We now know that individuals are not equally susceptible to disease. Individuals are unique in terms of their microbiota and the state of their immune system at any given time. The makeup of the resident microbiota can influence an individual's susceptibility to an infection. Members of the normal microbiota play an important role in immunity by inhibiting the growth of transient pathogens. In some cases, the microbiota may prevent a pathogen from establishing an infection; in others, it may not prevent an infection altogether but may influence the severity or type of signs and symptoms. As a result, two individuals with the same disease may not always present with the same signs and symptoms. In addition, some individuals have stronger immune systems than others. Individuals with immune systems weakened by age or an unrelated illness are much more susceptible to certain infections than individuals with strong immune systems.

Koch also assumed that all pathogens are microorganisms that can be grown in pure culture (postulate 2) and that animals could serve as reliable models for human disease. However, we now know that not all pathogens can be grown in pure culture, and many human diseases cannot be reliably replicated in animal hosts. Viruses and certain bacteria, including *Rickettsia* and *Chlamydia*, are obligate intracellular pathogens that can grow only when inside a host cell. If a microbe cannot be cultured, a researcher cannot move past postulate 2. Likewise, without a suitable nonhuman host, a researcher cannot evaluate postulate 2 without deliberately infecting humans, which presents obvious ethical concerns. AIDS is an example of such a disease because the human immunodeficiency virus (HIV) only causes disease in humans.

**Exercise 3.2.1**

- Briefly summarize the limitations of Koch's postulates.

## Molecular Koch's Postulates

In 1988, Stanley Falkow (1934–) proposed a revised form of Koch's postulates known as molecular Koch's postulates. These are listed in the left column of ***Table*** 3.2.2. The premise for molecular Koch's postulates is not in the ability to isolate a particular pathogen but rather to identify a gene that may cause the organism to be pathogenic.

Falkow's modifications to Koch's original postulates explain not only infections caused by intracellular pathogens but also the existence of pathogenic strains of organisms that are usually nonpathogenic. For example, the predominant form of the bacterium Escherichia coli is a member of the normal microbiota of the human intestine and is generally considered harmless. However, there are pathogenic strains of *E. coli* such as enterotoxigenic *E. coli* (ETEC) and enterohemorrhagic *E. coli* (O157:H7) (EHEC). We now know ETEC and EHEC exist because of the acquisition of new genes by the once-harmless E. coli, which, in the form of these pathogenic strains, is now capable of producing toxins and causing illness. The pathogenic forms resulted from minor genetic changes. The right-side column of ***Table*** 3.2.2 illustrates how molecular Koch's postulates can be applied to identify EHEC as a pathogenic bacterium.

*Table 3.2.2: Molecular Koch's Postulates Applied to EHEC*

| Molecular Koch's Postulates | Application to EHEC |
|---|---|
| (1) The phenotype (sign or symptom of disease) should be associated only with pathogenic strains of a species. | EHEC causes intestinal inflammation and diarrhea, whereas nonpathogenic strains of *E. coli* do not. |
| (2) Inactivation of the suspected gene(s) associated with pathogenicity should result in a measurable loss of pathogenicity. | One of the genes in EHEC encodes for Shiga toxin, a bacterial toxin (poison) that inhibits protein synthesis. Inactivating this gene reduces the bacteria's ability to cause disease. |

| Molecular Koch's Postulates | Application to EHEC |
|---|---|
| (3) Reversion of the inactive gene should restore the disease phenotype. | By adding the gene that encodes the toxin back into the genome (e.g., with a phage or plasmid), EHEC's ability to cause disease is restored. |

As with Koch's original postulates, the molecular Koch's postulates have limitations. For example, genetic manipulation of some pathogens is not possible using current methods of molecular genetics. In a similar vein, some diseases do not have suitable animal models, which limits the utility of both the original and molecular postulates.

**Exercise 3.2.2**

- Explain the differences between Koch's original postulates and the molecular Koch's postulates.

## Pathogenicity and Virulence

The ability of a microbial agent to cause disease is called **pathogenicity**, and the degree to which an organism is pathogenic is called **virulence**. Virulence is a continuum. On one end of the spectrum are organisms that are avirulent (not harmful) and on the other are organisms that are highly virulent. Highly virulent pathogens will almost always lead to a disease state when introduced to the body, and some may even cause multi-organ and body system failure in healthy individuals. Less virulent pathogens may cause an initial infection, but may not always cause severe illness. Pathogens with low virulence would more likely result in mild signs and symptoms of disease, such as low-grade fever, headache, or muscle aches. Some individuals might even be asymptomatic.

An example of a highly virulent microorganism is *Bacillus anthracis*, the pathogen responsible for anthrax. B. *anthracis* can produce different forms of disease, depending on the route of transmission (e.g., cutaneous injection, inhalation, ingestion). The most serious form of anthrax is inhalation anthrax. After B. *anthracis* spores are inhaled, they germinate. An active infection develops and the bacteria release potent toxins that cause edema (fluid buildup in tissues), hypoxia (a condition preventing oxygen from reaching tissues), and necrosis (cell death and inflammation). Signs and symptoms of inhalation anthrax include high fever, difficulty breathing, vomiting and coughing up blood, and severe chest pains suggestive of a heart attack. With inhalation anthrax, the toxins and bacteria enter the bloodstream, which can lead to multi-organ failure and death of the patient. If a gene (or genes) involved in pathogenesis is inactivated, the bacteria become less virulent or nonpathogenic.

Virulence of a pathogen can be quantified using controlled experiments with laboratory animals. Two important indicators of virulence are the **median infectious dose ($ID_{50}$)** and **the median lethal dose ($LD_{50}$)**, both of which are typically determined experimentally using animal models. The $ID_{50}$ is the number of pathogen cells or virions required to cause active infection in 50% of inoculated animals. The $LD_{50}$ is the number of pathogenic cells, virions, or amount of toxin required to kill 50% of infected animals. To calculate these values, each group of animals is inoculated with one of a range of known numbers of pathogen cells or virions. In graphs like the one shown in ***Figure*** 3.2.2, the percentage of animals that have been infected (for $ID_{50}$) or killed (for $LD_{50}$) is plotted against the concentration of pathogen inoculated. ***Figure*** 3.2.2 represents data graphed from a hypothetical experiment measuring the $LD_{50}$ of a pathogen. Interpretation of the data from this graph indicates that the $LD_{50}$ of the pathogen for the test animals is 104 pathogen cells or virions (depending upon the pathogen studied).

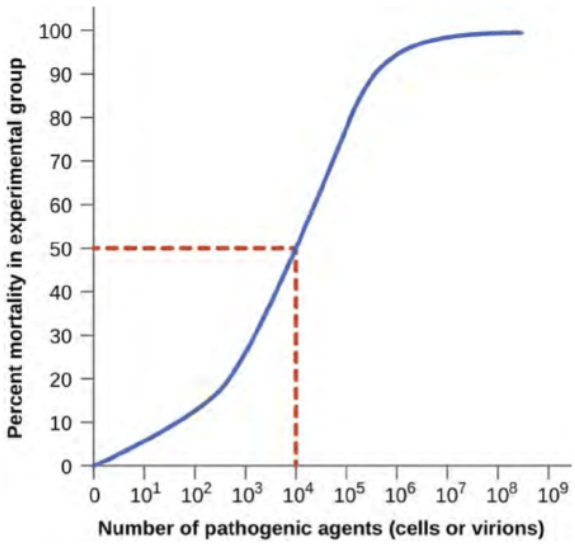



Figure 3.2.2: A graph like this is used to determine $LD_{50}$ by plotting pathogen concentration against the percent of infected test animals that have died. In this example, the $LD_{50} = 10^4$ pathogenic particles.

***Table*** 3.2.3 lists selected foodborne pathogens and their $ID_{50}$ values in humans (as determined from epidemiologic data and studies on human volunteers). Keep in mind that these are median values. The actual infective dose for an individual can vary widely, depending on factors such as route of entry; the age, health, and immune status of the host; and environmental and pathogen-specific factors such as susceptibility to the acidic pH of the stomach. It is also important to note that a pathogen's infective dose does not necessarily correlate with disease severity. For example, just a single cell of *Salmonella* enterica serotype Typhimurium can result in an active infection. The resultant disease, *Salmonella* gastroenteritis or salmonellosis, can cause nausea, vomiting, and diarrhea, but has a mortality rate of less than 1% in healthy adults. In contrast, *S. enterica* serotype Typhi has a much higher $ID_{50}$, typically requiring as many as 1,000 cells to produce infection. However, this serotype causes typhoid fever, a much more systemic and severe disease that has a mortality rate as high as 10% in untreated individuals.

*Table 3.2.3: $ID_{50}$ for Selected Foodborne Diseases*[1]

| Pathogen | $ID_{50}$ |
|---|---|
| Viruses | |
| Hepatitis A virus | 10–100 |
| Norovirus | 1–10 |
| Rotavirus | 10–100 |
| Bacteria | |
| *Escherichia coli*, enterohemorrhagic (EHEC, serotype O157) | 10–100 |
| *E. coli*, enteroinvasive (EIEC) | 200–5,000 |
| *E. coli*, enteropathogenic (EPEC) | 10,000,000–10,000,000,000 |
| *E. coli*, enterotoxigenic (ETEC) | 10,000,000–10,000,000,000 |
| *Salmonella enterica* serovar Typhi | <1,000 |
| *S. enterica* serovar Typhimurium | ≥1 |
| *Shigella dysenteriae* | 10–200 |
| *Vibrio cholerae* (serotypes O139, O1) | 1,000,000 |
| *V. parahemolyticus* | 100,000,000 |
| Protozoa | |

| Pathogen | $ID_{50}$ |
|---|---|
| *Giardia lamblia* | 1 |
| *Cryptosporidium parvum* | 10–100 |

**Exercise 3.2.3**

- What is the difference between a pathogen's infective dose and lethal dose?
- Which is more closely related to the severity of a disease?

## Primary Pathogens versus Opportunistic Pathogens

Pathogens can be classified as either primary pathogens or opportunistic pathogens. A **primary pathogen** can cause disease in a host regardless of the host's resident microbiota or immune system. An **opportunistic pathogen**, by contrast, can only cause disease in situations that compromise the host's defenses, such as the body's protective barriers, immune system, or normal microbiota. Individuals susceptible to opportunistic infections include the very young, the elderly, women who are pregnant, patients undergoing chemotherapy, people with immunodeficiencies (such as acquired immunodeficiency syndrome [AIDS]), patients who are recovering from surgery, and those who have had a breach of protective barriers (such as a severe wound or burn).

An example of a primary pathogen is enterohemorrhagic *E. coli* (EHEC), which produces a virulence factor known as Shiga toxin. This toxin inhibits protein synthesis, leading to severe and bloody diarrhea, inflammation, and renal failure, even in patients with healthy immune systems. *Staphylococcus epidermidis*, on the other hand, is an opportunistic pathogen that is among the most frequent causes of nosocomial disease.[2] *S. epidermidis* is a member of the normal microbiota of the skin, where it is generally avirulent. However, in hospitals, it can also grow in biofilms that form on catheters, implants, or other devices that are inserted into the body during surgical procedures. Once inside the body, *S. epidermidis* can cause serious infections such as endocarditis, and it produces virulence factors that promote the persistence of such infections.

Other members of the normal microbiota can also cause opportunistic infections under certain conditions. This often occurs when microbes that reside harmlessly in one body location end up in a different body system, where they cause disease. For example, *E. coli* normally found in the large intestine can cause a urinary tract infection if it enters the bladder. This is the leading cause of urinary tract infections among women.

Members of the normal microbiota may also cause disease when a shift in the environment of the body leads to overgrowth of a particular microorganism. For example, the yeast *Candida* is part of the normal microbiota of the skin, mouth, intestine, and vagina, but its population is kept in check by other organisms of the microbiota. If an individual is taking antibacterial medications, however, bacteria that would normally inhibit the growth of *Candida* can be killed off, leading to a sudden growth in the population of *Candida*, which is not affected by antibacterial medications because it is a fungus. An overgrowth of *Candida* can manifest as oral thrush (growth on mouth, throat, and tongue), a vaginal yeast infection, or cutaneous candidiasis. Other scenarios can also provide opportunities for *Candida* infections. Untreated diabetes can result in a high concentration of glucose in the saliva, which provides an optimal environment for the growth of *Candida*, resulting in thrush. Immunodeficiencies such as those seen in patients with HIV, AIDS, and cancer also lead to higher incidence of thrush. Vaginal yeast infections can result from decreases in estrogen levels during the menstruation or menopause. The amount of glycogen available to lactobacilli in the vagina is controlled by levels of estrogen; when estrogen levels are low, lactobacilli produce less lactic acid. The resultant increase in vaginal pH allows overgrowth of *Candida* in the vagina.

**Exercise 3.2.4**

- Explain the difference between a primary pathogen and an opportunistic pathogen.
- Describe some conditions under which an opportunistic infection can occur.

# Stages of Pathogenesis

To cause disease, a pathogen must successfully achieve four steps or stages of pathogenesis: exposure (contact), adhesion (colonization), invasion, and infection. The pathogen must be able to gain entry to the host, travel to the location where it can establish an infection, evade or overcome the host's immune response, and cause damage (i.e., disease) to the host. In many cases, the cycle is completed when the pathogen exits the host and is transmitted to a new host.

## Exposure

An encounter with a potential pathogen is known as **exposure** or **contact**. The food we eat and the objects we handle are all ways that we can come into contact with potential pathogens. Yet, not all contacts result in infection and disease. For a pathogen to cause disease, it needs to be able to gain access into host tissue. An anatomic site through which pathogens can pass into host tissue is called a **portal of entry**. These are locations where the host cells are in direct contact with the external environment. Major portals of entry are identified in ***Figure*** 3.2.3 and include the skin, mucous membranes, and parenteral routes.

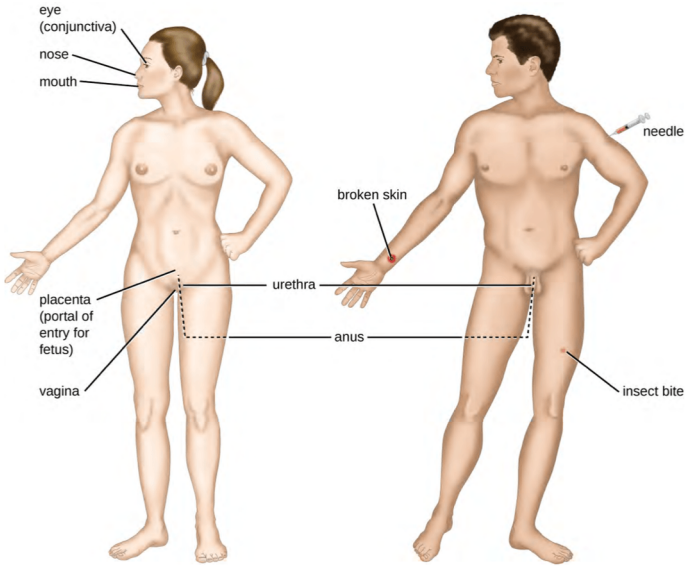



Figure 3.2.3: Shown are different portals of entry where pathogens can gain access into the body. With the exception of the placenta, many of these locations are directly exposed to the external environment.

Mucosal surfaces are the most important portals of entry for microbes; these include the mucous membranes of the respiratory tract, the gastrointestinal tract, and the genitourinary tract. Although most mucosal surfaces are in the interior of the body, some are contiguous with the external skin at various body openings, including the eyes, nose, mouth, urethra, and anus.

Most pathogens are suited to a particular portal of entry. A pathogen's portal specificity is determined by the organism's environmental adaptions and by the enzymes and toxins they secrete. The respiratory and gastrointestinal tracts are particularly vulnerable portals of entry because particles that include microorganisms are constantly inhaled or ingested, respectively.

Pathogens can also enter through a breach in the protective barriers of the skin and mucous membranes. Pathogens that enter the body in this way are said to enter by the **parenteral route**. For example, the skin is a good natural barrier to pathogens, but breaks in the skin (e.g., wounds, insect bites, animal bites, needle pricks) can provide a parenteral portal of entry for microorganisms.

In pregnant women, the placenta normally prevents microorganisms from passing from the mother to the fetus. However, a few pathogens are capable of crossing the blood-placental barrier. The gram-positive bacterium *Listeria monocytogenes*, which causes the foodborne disease listeriosis, is one example that poses a serious risk to the fetus and can sometimes lead to spontaneous abortion. Other pathogens that can pass the placental barrier to infect the fetus are known collectively by the acronym TORCH (***Table*** 3.2.4).

Transmission of infectious diseases from mother to baby is also a concern at the time of birth when the baby passes through the birth canal. Babies whose mothers have active chlamydia or gonorrhea infections may be exposed to the causative pathogens in the vagina, which can result in eye infections that lead to blindness. To prevent this, it is standard practice to administer antibiotic

drops to infants' eyes shortly after birth.

*Table 3.2.4: Pathogens Capable of Crossing the Placental Barrier (TORCH Infections)*

| | Disease | Pathogen |
|---|---|---|
| **T** | Toxoplasmosis | *Toxoplasma gondii* (protozoan) |
| **O**[3] | Syphilis | *Treponema pallidum* (bacterium) |
| | Chickenpox | Varicella-zoster virus (human herpesvirus 3) |
| | Hepatitis B | Hepatitis B virus (hepadnavirus) |
| | HIV | Retrovirus |
| | Fifth disease (erythema infectiosum) | Parvovirus B19 |
| **R** | Rubella (German measles) | Togavirus |
| **C** | Cytomegalovirus | Human herpesvirus 5 |
| **H** | Herpes | Herpes simplex viruses (HSV) 1 and 2 |

Clinical Focus

**Part 2**

At the clinic, a physician takes down Michael's medical history and asks about his activities and diet over the past week. Upon learning that Michael became sick the day after the party, the physician orders a blood test to check for pathogens associated with foodborne diseases. After tests confirm that presence of a gram-positive rod in Michael's blood, he is given an injection of a broad-spectrum antibiotic and sent to a nearby hospital, where he is admitted as a patient. There he is to receive additional intravenous antibiotic therapy and fluids.

- Is this bacterium in Michael's blood part of normal microbiota?
- What portal of entry did the bacteria use to cause this infection?

*Jump to the next Clinical Focus box. Go back to the previous Clinical Focus box.*

## Adhesion

Following the initial exposure, the pathogen adheres at the portal of entry. The term **adhesion** refers to the capability of pathogenic microbes to attach to the cells of the body using adhesion factors, and different pathogens use various mechanisms to adhere to the cells of host tissues.

Molecules (either proteins or carbohydrates) called **adhesins** are found on the surface of certain pathogens and bind to specific receptors (glycoproteins) on host cells. Adhesins are present on the fimbriae and flagella of bacteria, the cilia of protozoa, and the capsids or membranes of viruses. Protozoans can also use hooks and barbs for adhesion; spike proteins on viruses also enhance viral adhesion. The production of glycocalyces (slime layers and capsules) (***Figure*** 3.2.4), with their high sugar and protein content, can also allow certain bacterial pathogens to attach to cells.

Biofilm growth can also act as an adhesion factor. A biofilm is a community of bacteria that produce a glycocalyx, known as extrapolymeric substance (EPS), that allows the biofilm to attach to a surface. Persistent Pseudomonas aeruginosa infections are common in patients suffering from cystic fibrosis, burn wounds, and middle-ear infections (otitis media) because P. aeruginosa produces a biofilm. The EPS allows the bacteria to adhere to the host cells and makes it harder for the host to physically remove the pathogen. The EPS not only allows for attachment but provides protection against the immune system and antibiotic treatments, preventing antibiotics from reaching the bacterial cells within the biofilm. In addition, not all bacteria in a biofilm are rapidly growing; some are in stationary phase. Since antibiotics are most effective against rapidly growing bacteria, portions of

bacteria in a biofilm are protected against antibiotics.[4]

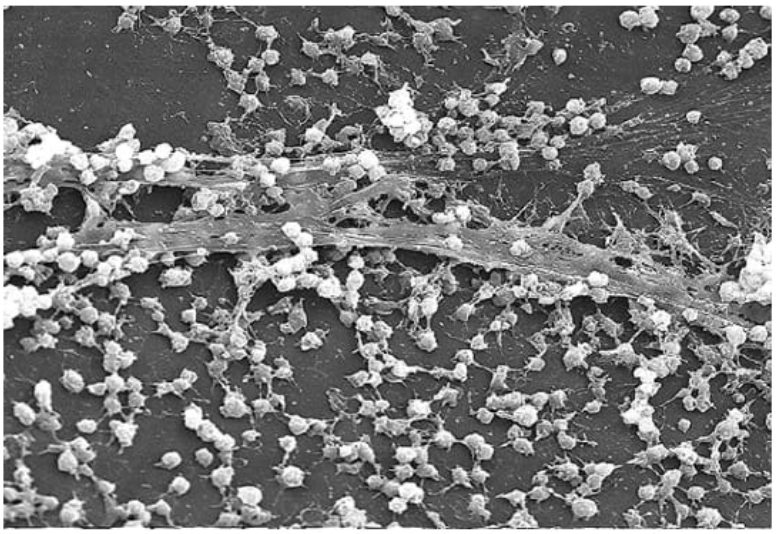


Figure 3.2.4: Glycocalyx produced by bacteria in a biofilm allows the cells to adhere to host tissues and to medical devices such as the catheter surface shown here. (credit: modification of work by Centers for Disease Control and Prevention)

## Invasion

Once adhesion is successful, **invasion** can proceed. Invasion involves the dissemination of a pathogen throughout local tissues or the body. Pathogens may produce exoenzymes or toxins, which serve as virulence factors that allow them to colonize and damage host tissues as they spread deeper into the body. Pathogens may also produce virulence factors that protect them against immune system defenses. A pathogen's specific virulence factors determine the degree of tissue damage that occurs. ***Figure*** 3.2.5 shows the invasion of *H. pylori* into the tissues of the stomach, causing damage as it progresses.

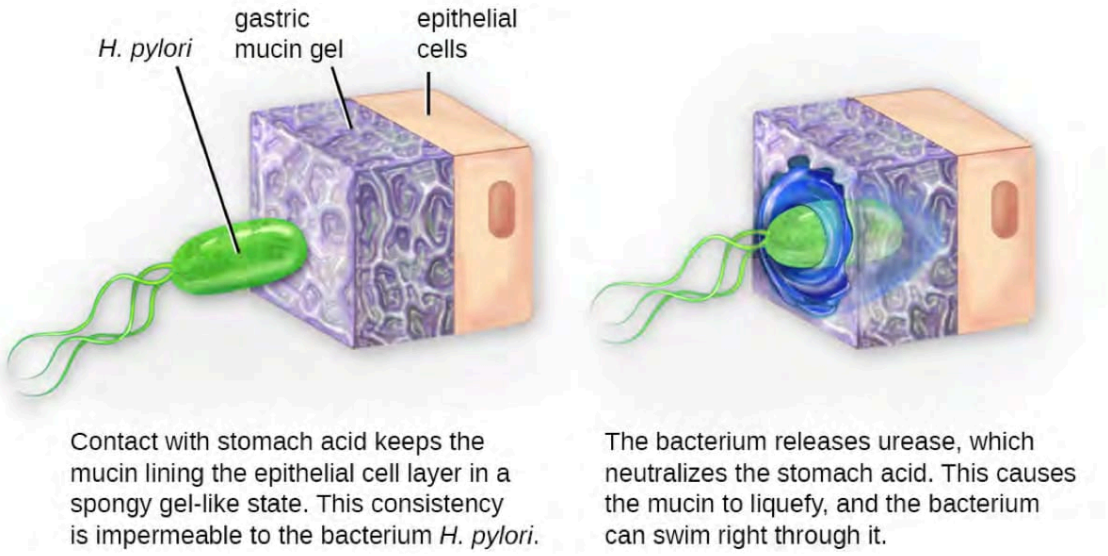



Figure 3.2.5: *H. pylori* is able to invade the lining of the stomach by producing virulence factors that enable it pass through the mucin layer covering epithelial cells. (credit: modification of work by Zina Deretsky, National Science Foundation)

Intracellular pathogens achieve invasion by entering the host's cells and reproducing. Some are obligate intracellular pathogens (meaning they can only reproduce inside of host cells) and others are facultative intracellular pathogens (meaning they can reproduce either inside or outside of host cells). By entering the host cells, intracellular pathogens are able to evade some mechanisms of the immune system while also exploiting the nutrients in the host cell.

Entry to a cell can occur by endocytosis. For most kinds of host cells, pathogens use one of two different mechanisms for endocytosis and entry. One mechanism relies on effector proteins secreted by the pathogen; these effector proteins trigger entry into the host cell. This is the method that *Salmonella* and *Shigella* use when invading intestinal epithelial cells. When these pathogens come in contact with epithelial cells in the intestine, they secrete effector molecules that cause protrusions of membrane ruffles that bring the bacterial cell in. This process is called membrane ruffling. The second mechanism relies on surface proteins expressed on the pathogen that bind to receptors on the host cell, resulting in entry. For example, *Yersinia pseudotuberculosis* produces a surface protein known as invasin that binds to beta-1 integrins expressed on the surface of host cells.

Some host cells, such as white blood cells and other phagocytes of the immune system, actively endocytose pathogens in a process called phagocytosis. Although phagocytosis allows the pathogen to gain entry to the host cell, in most cases, the host cell kills and degrades the pathogen by using digestive enzymes. Normally, when a pathogen is ingested by a phagocyte, it is enclosed within a phagosome in the cytoplasm; the phagosome fuses with a lysosome to form a phagolysosome, where digestive enzymes kill the pathogen (see Pathogen Recognition and Phagocytosis). However, some intracellular pathogens have the ability to survive and multiply within phagocytes. Examples include *Listeria monocytogenes* and *Shigella*; these bacteria produce proteins that lyse the phagosome before it fuses with the lysosome, allowing the bacteria to escape into the phagocyte's cytoplasm where they can multiply. Bacteria such as *Mycobacterium tuberculosis*, *Legionella pneumophila*, and *Salmonella* species use a slightly different mechanism to evade being digested by the phagocyte. These bacteria prevent the fusion of the phagosome with the lysosome, thus remaining alive and dividing within the phagosome.

## Infection

Following invasion, successful multiplication of the pathogen leads to infection. Infections can be described as local, focal, or systemic, depending on the extent of the infection. A **local infection** is confined to a small area of the body, typically near the portal of entry. For example, a hair follicle infected by *Staphylococcus aureus* infection may result in a boil around the site of infection, but the bacterium is largely contained to this small location. Other examples of local infections that involve more extensive tissue involvement include urinary tract infections confined to the bladder or pneumonia confined to the lungs.

In a **focal infection**, a localized pathogen, or the toxins it produces, can spread to a secondary location. For example, a dental hygienist nicking the gum with a sharp tool can lead to a local infection in the gum by *Streptococcus* bacteria of the normal oral microbiota. These *Streptococcus* spp. may then gain access to the bloodstream and make their way to other locations in the body, resulting in a secondary infection.

When an infection becomes disseminated throughout the body, we call it a **systemic infection**. For example, infection by the varicella-zoster virus typically gains entry through a mucous membrane of the upper respiratory system. It then spreads throughout the body, resulting in the classic red skin lesions associated with chickenpox. Since these lesions are not sites of initial infection, they are signs of a systemic infection.

Sometimes a **primary infection**, the initial infection caused by one pathogen, can lead to a **secondary infection** by another pathogen. For example, the immune system of a patient with a primary infection by HIV becomes compromised, making the patient more susceptible to secondary diseases like oral thrush and others caused by opportunistic pathogens. Similarly, a primary infection by Influenzavirus damages and decreases the defense mechanisms of the lungs, making patients more susceptible to a secondary pneumonia by a bacterial pathogen like *Haemophilus influenzae* or *Streptococcus pneumoniae*. Some secondary infections can even develop as a result of treatment for a primary infection. Antibiotic therapy targeting the primary pathogen can cause collateral damage to the normal microbiota, creating an opening for opportunistic pathogens (see Case in Point: A Secondary Yeast Infection).

Case in Point

**A Secondary Yeast Infection**

Anita, a 36-year-old mother of three, goes to an urgent care center complaining of pelvic pressure, frequent and painful urination, abdominal cramps, and occasional blood-tinged urine. Suspecting a urinary tract infection (UTI), the physician requests a urine sample and sends it to the lab for a urinalysis. Since it will take approximately 24 hours to get the results of the culturing, the physician immediately starts Anita on the antibiotic ciprofloxacin. The next day, the microbiology

lab confirms the presence of *E. coli* in Anita's urine, which is consistent with the presumptive diagnosis. However, the antimicrobial susceptibility test indicates that ciprofloxacin would not effectively treat Anita's UTI, so the physician prescribes a different antibiotic.

After taking her antibiotics for 1 week, Anita returns to the clinic complaining that the prescription is not working. Although the painful urination has subsided, she is now experiencing vaginal itching, burning, and discharge. After a brief examination, the physician explains to Anita that the antibiotics were likely successful in killing the *E. coli* responsible for her UTI; however, in the process, they also wiped out many of the "good" bacteria in Anita's normal microbiota. The new symptoms that Anita has reported are consistent with a secondary yeast infection by *Candida albicans*, an opportunistic fungus that normally resides in the vagina but is inhibited by the bacteria that normally reside in the same environment.

To confirm this diagnosis, a microscope slide of a direct vaginal smear is prepared from the discharge to check for the presence of yeast. A sample of the discharge accompanies this slide to the microbiology lab to determine if there has been an increase in the population of yeast causing vaginitis. After the microbiology lab confirms the diagnosis, the physician prescribes an antifungal drug for Anita to use to eliminate her secondary yeast infection.

• Why was Candida not killed by the antibiotics prescribed for the UTI?

**Exercise 3.2.5**

- List three conditions that could lead to a secondary infection

## Transmission of Disease

For a pathogen to persist, it must put itself in a position to be transmitted to a new host, leaving the infected host through a **portal of exit** (***Figure*** 3.2.6). As with portals of entry, many pathogens are adapted to use a particular portal of exit. Similar to portals of entry, the most common portals of exit include the skin and the respiratory, urogenital, and gastrointestinal tracts. Coughing and sneezing can expel pathogens from the respiratory tract. A single sneeze can send thousands of virus particles into the air. Secretions and excretions can transport pathogens out of other portals of exit. Feces, urine, semen, vaginal secretions, tears, sweat, and shed skin cells can all serve as vehicles for a pathogen to leave the body. Pathogens that rely on insect vectors for transmission exit the body in the blood extracted by a biting insect. Similarly, some pathogens exit the body in blood extracted by needles.

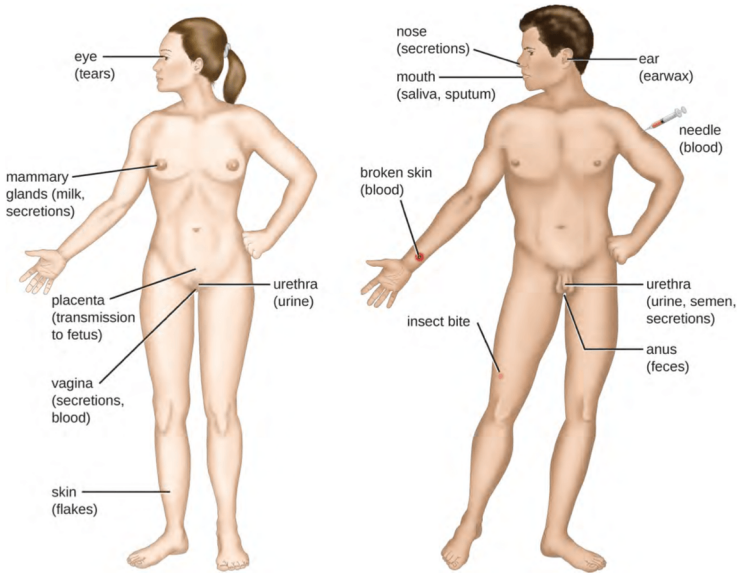



Figure 3.2.6: Pathogens leave the body of an infected host through various portals of exit to infect new hosts.

## Key Concepts and Summary

- **Koch's postulates** are used to determine whether a particular microorganism is a pathogen. **Molecular Koch's postulates** are used to determine what genes contribute to a pathogen's ability to cause disease.
- **Virulence**, the degree to which a pathogen can cause disease, can be quantified by calculating either the $\mathbf{ID}_{50}$ or $\mathbf{LD}_{50}$ of a pathogen on a given population.
- **Primary pathogens** are capable of causing pathological changes associated with disease in a healthy individual, whereas **opportunistic pathogens** can only cause disease when the individual is compromised by a break in protective barriers or immunosuppression.
- Infections and disease can be caused by pathogens in the environment or microbes in an individual's **resident microbiota**.
- Infections can be classified as **local**, **focal**, or **systemic** depending on the extent to which the pathogen spreads in the body.
- A **secondary infection** can sometimes occur after the host's defenses or normal microbiota are compromised by a **primary infection** or antibiotic treatment.
- Pathogens enter the body through **portals of entry** and leave through portals of exit. The stages of pathogenesis include **exposure**, **adhesion**, **invasion**, **infection**, and **transmission**.

## Footnotes

1. Food and Drug Administration. "Bad Bug Book, Foodborne Pathogenic Microorganisms and Natural Toxins." 2nd ed. Silver Spring, MD: US Food and Drug Administration; 2012.
2. M. Otto. "*Staphylococcus epidermidis*--The 'Accidental' Pathogen." *Nature Reviews Microbiology* 7 no. 8 (2009):555–567.
3. The O in TORCH stands for "other.
4. D. Davies. "Understanding Biofilm Resistance to Antibacterial Agents." *Nature Reviews Drug Discovery* 2 (2003):114–122.

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# 3.3: Virulence Factors of Bacterial and Viral Pathogens

## Learning Objectives

- Explain how virulence factors contribute to signs and symptoms of infectious disease
- Differentiate between endotoxins and exotoxins
- Describe and differentiate between various types of exotoxins
- Describe the mechanisms viruses use for adhesion and antigenic variation

In the previous section, we explained that some pathogens are more virulent than others. This is due to the unique **virulence factors** produced by individual pathogens, which determine the extent and severity of disease they may cause. A pathogen's virulence factors are encoded by genes that can be identified using molecular Koch's postulates. When genes encoding virulence factors are inactivated, virulence in the pathogen is diminished. In this section, we examine various types and specific examples of virulence factors and how they contribute to each step of pathogenesis.

## Virulence Factors for Adhesion

As discussed in the previous section, the first two steps in pathogenesis are exposure and adhesion. Recall that an adhesin is a protein or glycoprotein found on the surface of a pathogen that attaches to receptors on the host cell. Adhesins are found on bacterial, viral, fungal, and protozoan pathogens. One example of a bacterial adhesin is type 1 fimbrial adhesin, a molecule found on the tips of fimbriae of enterotoxigenic *E. coli* (ETEC). Recall that fimbriae are hairlike protein bristles on the cell surface. Type 1 fimbrial adhesin allows the fimbriae of ETEC cells to attach to the mannose glycans expressed on intestinal epithelial cells. ***Table*** 3.3.1 lists common adhesins found in some of the pathogens we have discussed or will be seeing later in this chapter.

*Table* 3.3.1*: Some Bacterial Adhesins and Their Host Attachment Sites*

| Pathogen | Disease | Adhesin | Attachment Site |
|---|---|---|---|
| *Streptococcus pyogenes* | Strep throat | Protein F | Respiratory epithelial cells |
| *Streptococcus mutans* | Dental caries | Adhesin P1 | Teeth |
| *Neisseria gonorrhoeae* | Gonorrhea | Type IV pili | Urethral epithelial cells |
| Enterotoxigenic *E. coli* (ETEC) | Traveler's diarrhea | Type 1 fimbriae | Intestinal epithelial cells |
| *Vibrio cholerae* | Cholera | N-methylphenylalanine pili | Intestinal epithelial cells |

## Clinical Focus

**Part 3**

The presence of bacteria in Michael's blood is a sign of infection, since blood is normally sterile. There is no indication that the bacteria entered the blood through an injury. Instead, it appears the portal of entry was the gastrointestinal route. Based on Michael's symptoms, the results of his blood test, and the fact that Michael was the only one in the family to partake of the hot dogs, the physician suspects that Michael is suffering from a case of listeriosis.

*Listeria monocytogenes*, the facultative intracellular pathogen that causes listeriosis, is a common contaminant in ready-to-eat foods such as lunch meats and dairy products. Once ingested, these bacteria invade intestinal epithelial cells and translocate to the liver, where they grow inside hepatic cells. Listeriosis is fatal in about one in five normal healthy people, and mortality rates are slightly higher in patients with pre-existing conditions that weaken the immune response. A cluster of virulence genes encoded on a pathogenicity island is responsible for the pathogenicity of *L. monocytogenes*. These genes are regulated by a transcriptional factor known as peptide chain release factor 1 (PrfA). One of the genes regulated by PrfA is *hyl*, which encodes a toxin known as listeriolysin O (LLO), which allows the bacterium to escape vacuoles upon entry into a host

cell. A second gene regulated by PrfA is *actA*, which encodes for a surface protein known as actin assembly-inducing protein (ActA). ActA is expressed on the surface of *Listeria* and polymerizes host actin. This enables the bacterium to produce actin tails, move around the cell's cytoplasm, and spread from cell to cell without exiting into the extracellular compartment.

Michael's condition has begun to worsen. He is now experiencing a stiff neck and hemiparesis (weakness of one side of the body). Concerned that the infection is spreading, the physician decides to conduct additional tests to determine what is causing these new symptoms.

- What kind of pathogen causes listeriosis, and what virulence factors contribute to the signs and symptoms Michael is experiencing?
- Is it likely that the infection will spread from Michael's blood? If so, how might this explain his new symptoms?

Jump to the next Clinical Focus box. Go back to the previous Clinical Focus box.

## Bacterial Exoenzymes and Toxins as Virulence Factors

After exposure and adhesion, the next step in pathogenesis is invasion, which can involve enzymes and toxins. Many pathogens achieve invasion by entering the bloodstream, an effective means of dissemination because blood vessels pass close to every cell in the body. The downside of this mechanism of dispersal is that the blood also includes numerous elements of the immune system. Various terms ending in –emia are used to describe the presence of pathogens in the bloodstream. The presence of bacteria in blood is called **bacteremia**. Bacteremia involving pyogens (pus-forming bacteria) is called pyemia. When viruses are found in the blood, it is called **viremia**. The term **toxemia** describes the condition when toxins are found in the blood. If bacteria are both present and multiplying in the blood, this condition is called septicemia.

Patients with septicemia are described as **septic**, which can lead to **shock**, a life-threatening decrease in blood pressure (systolic pressure <90 mm Hg) that prevents cells and organs from receiving enough oxygen and nutrients. Some bacteria can cause shock through the release of toxins (virulence factors that can cause tissue damage) and lead to low blood pressure. Gram-negative bacteria are engulfed by immune system phagocytes, which then release tumor necrosis factor, a molecule involved in inflammation and fever. Tumor necrosis factor binds to blood capillaries to increase their permeability, allowing fluids to pass out of blood vessels and into tissues, causing swelling, or edema (***Figure*** 3.3.1). With high concentrations of tumor necrosis factor, the inflammatory reaction is severe and enough fluid is lost from the circulatory system that blood pressure decreases to dangerously low levels. This can have dire consequences because the heart, lungs, and kidneys rely on normal blood pressure for proper function; thus, multi- organ failure, shock, and death can occur.



Figure 3.3.1: This patient has edema in the tissue of the right hand. Such swelling can occur when bacteria cause the release of pro-inflammatory molecules from immune cells and these molecules cause an increased permeability of blood vessels, allowing fluid to escape the bloodstream and enter tissue.

## Exoenzymes

Some pathogens produce extracellular enzymes, or exoenzymes, that enable them to invade host cells and deeper tissues. Exoenzymes have a wide variety of targets. Some general classes of exoenzymes and associated pathogens are listed in ***Table*** 3.3.2. Each of these exoenzymes functions in the context of a particular tissue structure to facilitate invasion or support its own growth and defend against the immune system. For example, **hyaluronidase** S, an enzyme produced by pathogens like *Staphylococcus aureus*, *Streptococcus pyogenes*, and *Clostridium perfringens*, degrades the glycoside hylauronan (hyaluronic acid), which acts as an intercellular cement between adjacent cells in connective tissue (***Figure*** 3.3.2). This allows the pathogen to pass through the tissue layers at the portal of entry and disseminate elsewhere in the body (***Figure*** 3.3.2).

*Table* 3.3.2: *Some Classes of Exoenzymes and Their Targets*

| Class | Example | Function |
|---|---|---|
| Glycohydrolases | Hyaluronidase S in *Staphylococcus aureus* | Degrades hyaluronic acid that cements cells together to promote spreading through tissues |
| Nucleases | DNAse produced by S. *aureus* | Degrades DNA released by dying cells (bacteria and host cells) that can trap the bacteria, thus promoting spread |
| Phospholipases | Phospholipase C of *Bacillus anthracis* | Degrades phospholipid bilayer of host cells, causing cellular lysis, and degrade membrane of phagosomes to enable escape into the cytoplasm |
| Proteases | Collagenase in *Clostridium perfringens* | Degrades collagen in connective tissue to promote spread |

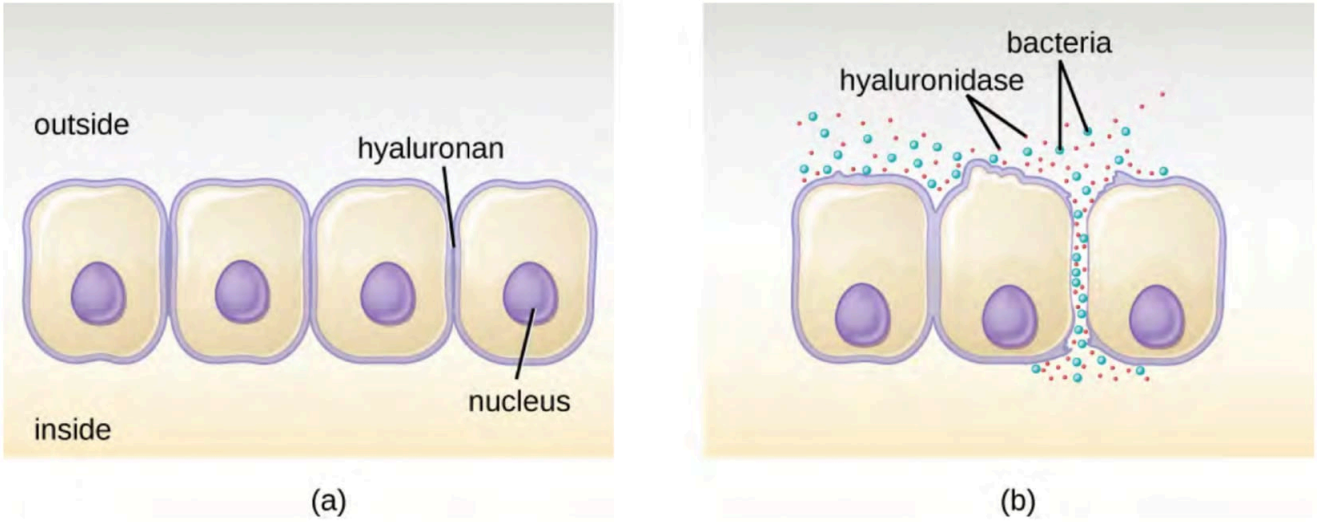



Figure 3.3.2: (a) Hyaluronan is a polymer found in the layers of epidermis that connect adjacent cells. (b) Hyaluronidase produced by bacteria degrades this adhesive polymer in the extracellular matrix, allowing passage between cells that would otherwise be blocked.

Pathogen-produced nucleases, such as **DNAse** produced by *S. aureus*, degrade extracellular DNA as a means of escape and spreading through tissue. As bacterial and host cells die at the site of infection, they lyse and release their intracellular contents. The DNA chromosome is the largest of the intracellular molecules, and masses of extracellular DNA can trap bacteria and prevent their spread. *S. aureus* produces a DNAse to degrade the mesh of extracellular DNA so it can escape and spread to adjacent tissues. This strategy is also used by *S. aureus* and other pathogens to degrade and escape webs of extracellular DNA produced by immune system phagocytes to trap the bacteria.

Enzymes that degrade the phospholipids of cell membranes are called phospholipases. Their actions are specific in regard to the type of phospholipids they act upon and where they enzymatically cleave the molecules. The pathogen responsible for anthrax, *B. anthracis*, produces phospholipase C. When *B. anthracis* is ingested by phagocytic cells of the immune system, phospholipase C degrades the membrane of the phagosome before it can fuse with the lysosome, allowing the pathogen to escape into the cytoplasm and multiply. Phospholipases can also target the membrane that encloses the phagosome within phagocytic cells. As described earlier in this chapter, this is the mechanism used by intracellular pathogens such as *L. monocytogenes* and *Rickettsia* to escape the phagosome and multiply within the cytoplasm of phagocytic cells. The role of phospholipases in bacterial virulence

is not restricted to phagosomal escape. Many pathogens produce phospholipases that act to degrade cell membranes and cause lysis of target cells. These phospholipases are involved in lysis of red blood cells, white blood cells, and tissue cells.

Bacterial pathogens also produce various protein-digesting enzymes, or proteases. Proteases can be classified according to their substrate target (e.g., serine proteases target proteins with the amino acid serine) or if they contain metals in their active site (e.g., zinc metalloproteases contain a zinc ion, which is necessary for enzymatic activity).

One example of a protease that contains a metal ion is the exoenzyme **collagenase**. Collagenase digests collagen, the dominant protein in connective tissue. Collagen can be found in the extracellular matrix, especially near mucosal membranes, blood vessels, nerves, and in the layers of the skin. Similar to hyaluronidase, collagenase allows the pathogen to penetrate and spread through the host tissue by digesting this connective tissue protein. The collagenase produced by the gram-positive bacterium *Clostridium perfringens*, for example, allows the bacterium to make its way through the tissue layers and subsequently enter and multiply in the blood (septicemia). *C. perfringens* then uses toxins and a phospholipase to cause cellular lysis and necrosis. Once the host cells have died, the bacterium produces gas by fermenting the muscle carbohydrates. The widespread necrosis of tissue and accompanying gas are characteristic of the condition known as gas gangrene (***Figure*** 3.3.3).

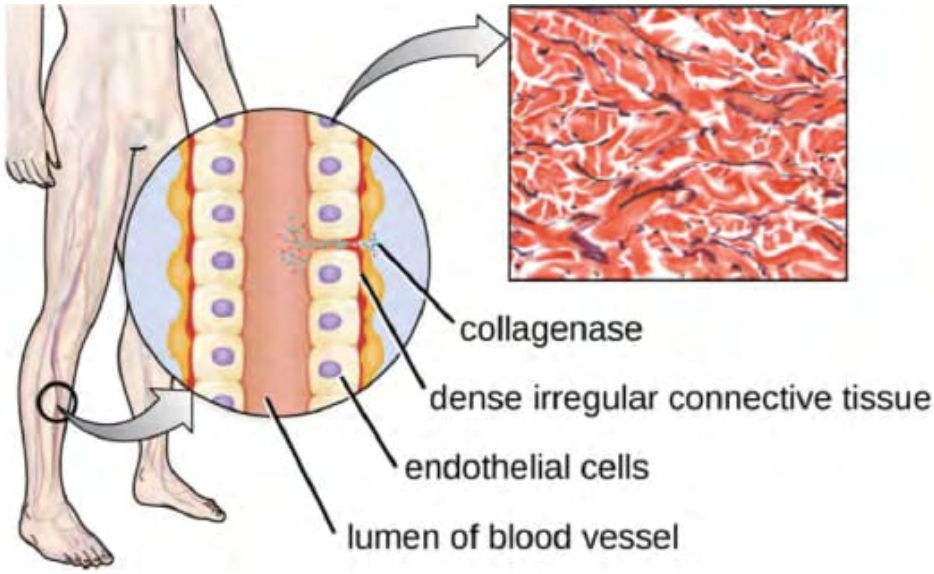



Figure 3.3.3: The illustration depicts a blood vessel with a single layer of endothelial cells surrounding the lumen and dense connective tissue (shown in red) surrounding the endothelial cell layer. Collagenase produced by *C. perfringens* degrades the collagen between the endothelial cells, allowing the bacteria to enter the bloodstream. (credit illustration: modification of work by Bruce Blaus; credit micrograph: Micrograph provided by the Regents of University of Michigan Medical School © 2012)

**Link to Learning**

Two types of cell death are apoptosis and necrosis. Visit this website to learn more about the differences between these mechanisms of cell death and their causes.

## Toxins

In addition to exoenzymes, certain pathogens are able to produce **toxins**, biological poisons that assist in their ability to invade and cause damage to tissues. The ability of a pathogen to produce toxins to cause damage to host cells is called **toxigenicity**.

Toxins can be categorized as endotoxins or exotoxins. The lipopolysaccharide (LPS) found on the outer membrane of gram-negative bacteria is called **endotoxin** (***Figure*** 3.3.4). During infection and disease, gram-negative bacterial pathogens release endotoxin either when the cell dies, resulting in the disintegration of the membrane, or when the bacterium undergoes binary fission. The lipid component of endotoxin, lipid A, is responsible for the toxic properties of the LPS molecule. Lipid A is relatively conserved across different genera of gram-negative bacteria; therefore, the toxic properties of lipid A are similar regardless of the gram-negative pathogen. In a manner similar to that of tumor necrosis factor, lipid A triggers the immune system's inflammatory response (see Inflammation and Fever). If the concentration of endotoxin in the body is low, the inflammatory response may

provide the host an effective defense against infection; on the other hand, high concentrations of endotoxin in the blood can cause an excessive inflammatory response, leading to a severe drop in blood pressure, multi-organ failure, and death.




Figure 3.3.4: Lipopolysaccharide is composed of lipid A, a core glycolipid, and an O-specific polysaccharide side chain. Lipid A is the toxic component that promotes inflammation and fever.

A classic method of detecting endotoxin is by using the Limulus amebocyte lysate (LAL) test. In this procedure, the blood cells (amebocytes) of the horseshoe crab (Limulus polyphemus) is mixed with a patient's serum. The amebocytes will react to the presence of any endotoxin. This reaction can be observed either chromogenically (color) or by looking for coagulation (clotting reaction) to occur within the serum. An alternative method that has been used is an enzyme-linked immunosorbent assay (ELISA) that uses antibodies to detect the presence of endotoxin.

Unlike the toxic lipid A of endotoxin, **exotoxins** are protein molecules that are produced by a wide variety of living pathogenic bacteria. Although some gram-negative pathogens produce exotoxins, the majority are produced by gram- positive pathogens. Exotoxins differ from endotoxin in several other key characteristics, summarized in ***Table*** 3.3.3. In contrast to endotoxin, which stimulates a general systemic inflammatory response when released, exotoxins are much more specific in their action and the cells they interact with. Each exotoxin targets specific receptors on specific cells and damages those cells through unique molecular mechanisms. Endotoxin remains stable at high temperatures, and requires heating at 121 °C (250 °F) for 45 minutes to inactivate. By contrast, most exotoxins are heat labile because of their protein structure, and many are denatured (inactivated) at temperatures above 41 °C (106 °F). As discussed earlier, endotoxin can stimulate a lethal inflammatory response at very high concentrations and has a measured $LD_{50}$ of 0.24 mg/kg. By contrast, very small concentrations of exotoxins can be lethal. For example, botulinum toxin, which causes botulism, has an $LD_{50}$ of 0.000001 mg/kg (240,000 times more lethal than endotoxin).

*Table 3.3.3: Comparison of Endotoxin and Exotoxins Produced by Bacteria*

| Characteristic | Endotoxin | Exotoxin |
|---|---|---|
| Source | Gram-negative bacteria | Gram-positive (primarily) and gram-negative bacteria |
| Composition | Lipid A component of lipopolysaccharide | Protein |
| Effect on host | General systemic symptoms of inflammation and fever | Specific damage to cells dependent upon receptor-mediated targeting of cells and specific mechanisms of action |
| Heat stability | Heat stable | Most are heat labile, but some are heat stable |
| $LD_{50}$ | High | Low |

The exotoxins can be grouped into three categories based on their target: intracellular targeting, membrane disrupting, and superantigens. ***Table*** 3.3.4 provides examples of well-characterized toxins within each of these three categories.

*Table 3.3.4: Some Common Exotoxins and Associated Bacterial Pathogens*

| Category | Example | Pathogen | Mechanism and Disease |
|---|---|---|---|
| Intracellular-targeting toxins | Cholera toxin | *Vibrio cholerae* | Activation of adenylate cyclase in intestinal cells, causing increased levels of cyclic adenosine monophosphate (cAMP) and secretion of fluids and electrolytes out of cell, causing diarrhea |
| | Tetanus toxin | *Clostridium tetani* | Inhibits the release of inhibitory neurotransmitters in the central nervous system, causing spastic paralysis |
| | Botulinum toxin | *Clostridium botulinum* | Inhibits release of the neurotransmitter acetylcholine from neurons, resulting in flaccid paralysis |

| Category | Example | Pathogen | Mechanism and Disease |
|---|---|---|---|
| | Diphtheria toxin | *Corynebacterium diphtheriae* | Inhibition of protein synthesis, causing cellular death |
| Membrane-disrupting toxins | Streptolysin | *Streptococcus pyogenes* | Proteins that assemble into pores in cell membranes, disrupting their function and killing the cell |
| | Pneumolysin | *Streptococcus pneumoniae* | |
| | Alpha-toxin | *Staphylococcus aureus* | |
| | Alpha-toxin | *Clostridium perfringens* | Phospholipases that degrade cell membrane phospholipids, disrupting membrane function and killing the cell |
| | Phospholipase C | *Pseudomonas aeruginosa* | |
| | Beta-toxin | *Staphylococcus aureus* | |
| Superantigens | Toxic shock syndrome toxin | *Staphylococcus aureus* | Stimulates excessive activation of immune system cells and release of cytokines (chemical mediators) from immune system cells. Life-threatening fever, inflammation, and shock are the result. |
| | Streptococcal mitogenic exotoxin | *Streptococcus pyogenes* | |
| | Streptococcal pyrogenic toxins | *Streptococcus pyogenes* | |

The **intracellular targeting toxins** comprise two components: A for activity and B for binding. Thus, these types of toxins are known as **A-B exotoxins** (***Figure*** 3.3.5). The B component is responsible for the cellular specificity of the toxin and mediates the initial attachment of the toxin to specific cell surface receptors. Once the A-B toxin binds to the host cell, it is brought into the cell by endocytosis and entrapped in a vacuole. The A and B subunits separate as the vacuole acidifies. The A subunit then enters the cell cytoplasm and interferes with the specific internal cellular function that it targets.

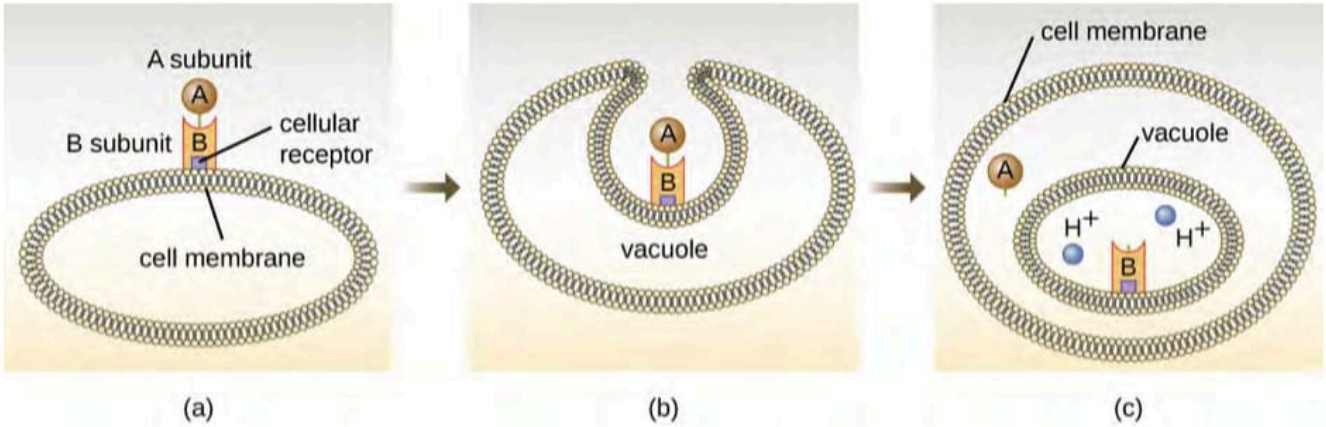



Figure 3.3.5: (a) In A-B toxins, the B component binds to the host cell through its interaction with specific cell surface receptors. (b) The toxin is brought in through endocytosis. (c) Once inside the vacuole, the A component (active component) separates from the B component and the A component gains access to the cytoplasm. (credit: modification of work by "Biology Discussion Forum"/YouTube)

Four unique examples of A-B toxins are the diphtheria, cholera, botulinum, and tetanus toxins. The diphtheria toxin is produced by the gram-positive bacterium *Corynebacterium diphtheriae*, the causative agent of nasopharyngeal and cutaneous diphtheria. After the A subunit of the diphtheria toxin separates and gains access to the cytoplasm, it facilitates the transfer of adenosine diphosphate (ADP)-ribose onto an elongation-factor protein (EF-2) that is needed for protein synthesis. Hence, diphtheria toxin

inhibits protein synthesis in the host cell, ultimately killing the cell (***Figure*** 3.3.6).

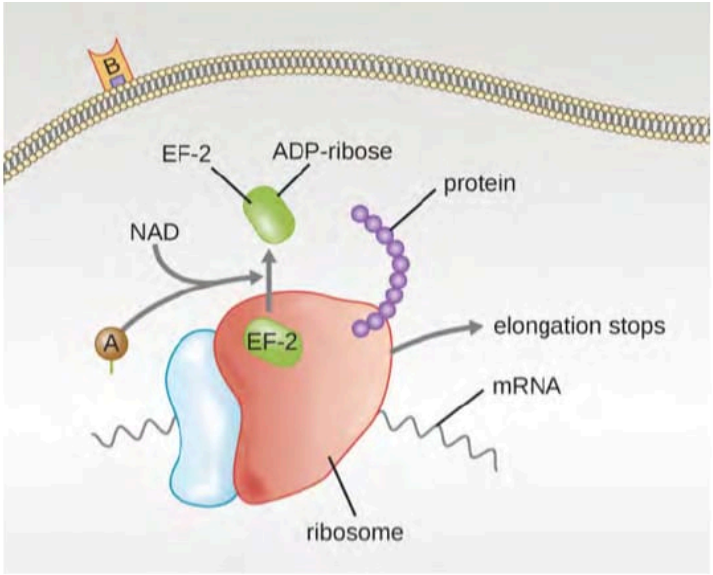



Figure 3.3.6: The mechanism of the diphtheria toxin inhibiting protein synthesis. The A subunit inactivates elongation factor 2 by transferring an ADP-ribose. This stops protein elongation, inhibiting protein synthesis and killing the cell.

Cholera toxin is an **enterotoxin** produced by the gram-negative bacterium *Vibrio cholerae* and is composed of one A subunit and five B subunits. The mechanism of action of the cholera toxin is complex. The B subunits bind to receptors on the intestinal epithelial cell of the small intestine. After gaining entry into the cytoplasm of the epithelial cell, the A subunit activates an intracellular G protein. The activated G protein, in turn, leads to the activation of the enzyme adenyl cyclase, which begins to produce an increase in the concentration of cyclic AMP (a secondary messenger molecule). The increased cAMP disrupts the normal physiology of the intestinal epithelial cells and causes them to secrete excessive amounts of fluid and electrolytes into the lumen of the intestinal tract, resulting in severe “rice-water stool” diarrhea characteristic of cholera.

*Botulinum* toxin (also known as botox) is a neurotoxin produced by the gram-positive bacterium *Clostridium botulinum*. It is the most acutely toxic substance known to date. The toxin is composed of a light A subunit and heavy protein chain B subunit. The B subunit binds to neurons to allow botulinum toxin to enter the neurons at the neuromuscular junction. The A subunit acts as a protease, cleaving proteins involved in the neuron’s release of acetylcholine, a neurotransmitter molecule. Normally, neurons release acetylcholine to induce muscle fiber contractions. The toxin’s ability to block acetylcholine release results in the inhibition of muscle contractions, leading to muscle relaxation. This has the potential to stop breathing and cause death. Because of its action, low concentrations of botox are used for cosmetic and medical procedures, including the removal of wrinkles and treatment of overactive bladder.

## Link to Learning

Click this link to see an animation of how the cholera toxin functions.

Click this link to see an animation of how the botulinum toxin functions.

Another neurotoxin is tetanus toxin, which is produced by the gram-positive bacterium *Clostridium tetani*. This toxin also has a light A subunit and heavy protein chain B subunit. Unlike botulinum toxin, tetanus toxin binds to inhibitory interneurons, which are responsible for release of the inhibitory neurotransmitters glycine and gamma-aminobutyric acid (GABA). Normally, these neurotransmitters bind to neurons at the neuromuscular junction, resulting in the inhibition of acetylcholine release. Tetanus toxin inhibits the release of glycine and GABA from the interneuron, resulting in permanent muscle contraction. The first symptom is typically stiffness of the jaw (lockjaw). Violent muscle spasms in other parts of the body follow, typically culminating with respiratory failure and death. ***Figure*** 3.3.7 shows the actions of both botulinum and tetanus toxins.

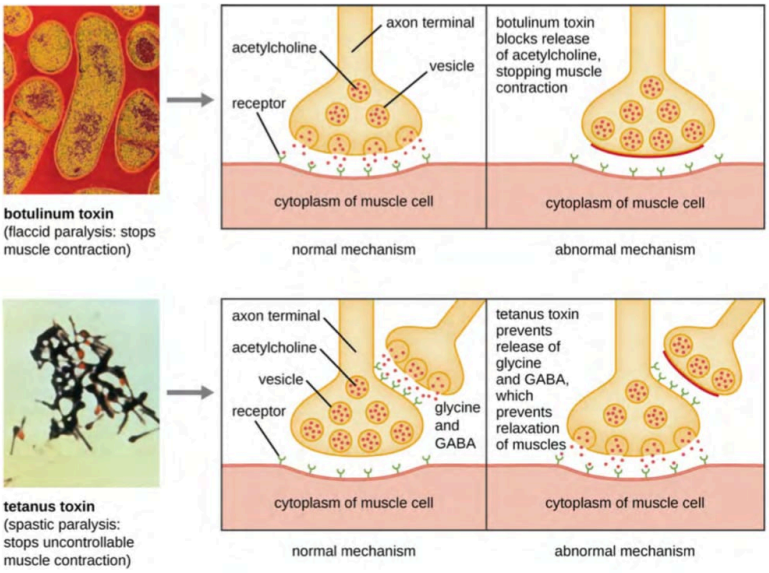



Figure 3.3.7: Mechanisms of botulinum and tetanus toxins. (credit micrographs: modification of work by Centers for Disease Control and Prevention)

Membrane-disrupting toxins affect cell membrane function either by forming pores or by disrupting the phospholipid bilayer in host cell membranes. Two types of membrane-disrupting exotoxins are **hemolysins** and leukocidins, which form pores in cell membranes, causing leakage of the cytoplasmic contents and cell lysis. These toxins were originally thought to target red blood cells (erythrocytes) and white blood cells (leukocytes), respectively, but we now know they can affect other cells as well. The gram-positive bacterium *Streptococcus pyogenes* produces streptolysins, water- soluble hemolysins that bind to the cholesterol moieties in the host cell membrane to form a pore. The two types of streptolysins, O and S, are categorized by their ability to cause hemolysis in erythrocytes in the absence or presence of oxygen. Streptolysin O is not active in the presence of oxygen, whereas streptolysin S is active in the presence of oxygen. Other important pore-forming membrane-disrupting toxins include alpha toxin of *Staphylococcus aureus* and pneumolysin of *Streptococcus pneumoniae*.

Bacterial phospholipases are **membrane-disrupting toxins** that degrade the phospholipid bilayer of cell membranes rather than forming pores. We have already discussed the phospholipases associated with *B. anthracis*, *L. pneumophila*, and *Rickettsia* species that enable these bacteria to effect the lysis of phagosomes. These same phospholipases are also hemolysins. Other phospholipases that function as hemolysins include the alpha toxin of *Clostridium perfringens*, phospholipase C of *P. aeruginosa*, and beta toxin of *Staphylococcus aureus*.

Some strains of S. *aureus* also produce a leukocidin called Panton-Valentine leukocidin (PVL). PVL consists of two subunits, S and F. The S component acts like the B subunit of an A-B exotoxin in that it binds to glycolipids on the outer plasma membrane of animal cells. The F-component acts like the A subunit of an A-B exotoxin and carries the enzymatic activity. The toxin inserts and assembles into a pore in the membrane. Genes that encode PVL are more frequently present in *S. aureus* strains that cause skin infections and pneumonia.[1] PVL promotes skin infections by causing edema, erythema (reddening of the skin due to blood vessel dilation), and skin necrosis. PVL has also been shown to cause necrotizing pneumonia. PVL promotes pro-inflammatory and cytotoxic effects on alveolar leukocytes. This results in the release of enzymes from the leukocytes, which, in turn, cause damage to lung tissue.

The third class of exotoxins is the **superantigens**. These are exotoxins that trigger an excessive, nonspecific stimulation of immune cells to secrete cytokines (chemical messengers). The excessive production of cytokines, often called a cytokine storm, elicits a strong immune and inflammatory response that can cause life-threatening high fevers, low blood pressure, multi-organ failure, shock, and death. The prototype superantigen is the toxic shock syndrome toxin of S. aureus. Most toxic shock syndrome cases are associated with vaginal colonization by toxin- producing S. aureus in menstruating women; however, colonization of other body sites can also occur. Some strains of Streptococcus pyogenes also produce superantigens; they are referred to as the streptococcal mitogenic exotoxins and the streptococcal pyrogenic toxins.

Exercise 3.3.1

- Describe how exoenzymes contribute to bacterial invasion.
- Explain the difference between exotoxins and endotoxin.
- Name the three classes of exotoxins.

## Virulence Factors for Survival in the Host and Immune Evasion

Evading the immune system is also important to invasiveness. Bacteria use a variety of virulence factors to evade phagocytosis by cells of the immune system. For example, many bacteria produce capsules, which are used in adhesion but also aid in immune evasion by preventing ingestion by phagocytes. The composition of the capsule prevents immune cells from being able to adhere and then phagocytose the cell. In addition, the capsule makes the bacterial cell much larger, making it harder for immune cells to engulf the pathogen (***Figure*** 3.3.8). A notable capsule-producing bacterium is the gram-positive pathogen *Streptococcus pneumoniae*, which causes pneumococcal pneumonia, meningitis, septicemia, and other respiratory tract infections. Encapsulated strains of S. *pneumoniae* are more virulent than nonencapsulated strains and are more likely to invade the bloodstream and cause septicemia and meningitis.

Some pathogens can also produce proteases to protect themselves against phagocytosis. As described in Adaptive Specific Host Defenses, the human immune system produces antibodies that bind to surface molecules found on specific bacteria (e.g., capsules, fimbriae, flagella, LPS). This binding initiates phagocytosis and other mechanisms of antibacterial killing and clearance. Proteases combat antibody-mediated killing and clearance by attacking and digesting the antibody molecules (***Figure*** 3.3.8).

In addition to capsules and proteases, some bacterial pathogens produce other virulence factors that allow them to evade the immune system. The fimbriae of certain species of *Streptococcus* contain M protein, which alters the surface of *Streptococcus* and inhibits phagocytosis by blocking the binding of the complement molecules that assist phagocytes in ingesting bacterial pathogens. The acid-fast bacterium *Mycobacterium tuberculosis* (the causative agent of tuberculosis) produces a waxy substance known as mycolic acid in its cell envelope. When it is engulfed by phagocytes in the lung, the protective mycolic acid coat enables the bacterium to resist some of the killing mechanisms within the phagolysosome.

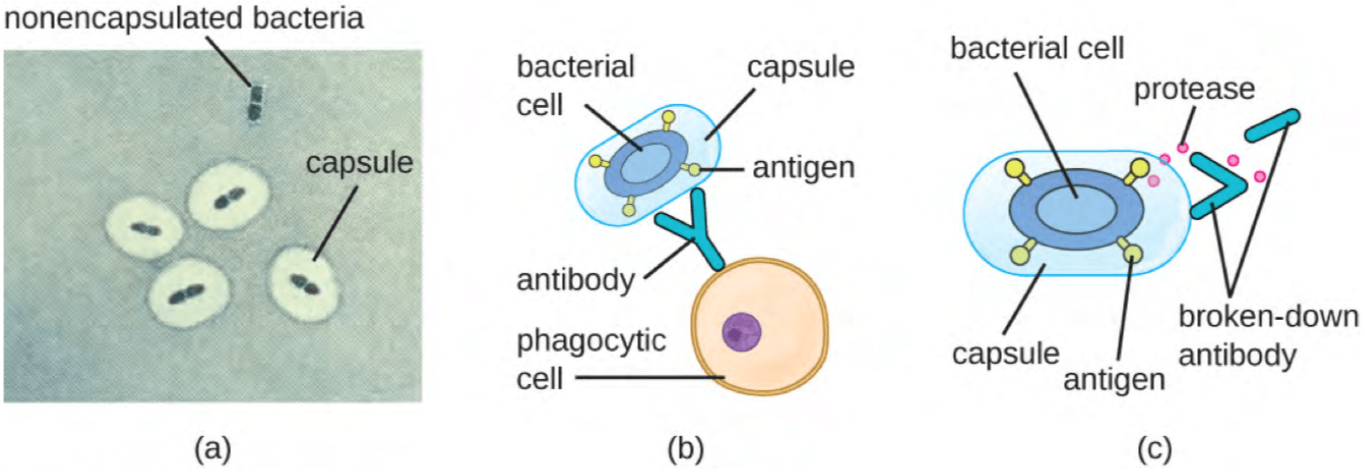



Figure 3.3.8: (a) A micrograph of capsules around bacterial cells. (b) Antibodies normally function by binding to antigens, molecules on the surface of pathogenic bacteria. Phagocytes then bind to the antibody, initiating phagocytosis. (c) Some bacteria also produce proteases, virulence factors that break down host antibodies to evade phagocytosis. (credit a: modification of work by Centers for Disease Control and Prevention)

Some bacteria produce virulence factors that promote infection by exploiting molecules naturally produced by the host. For example, most strains of *Staphylococcus* aureus produce the exoenzyme **coagulase**, which exploits the natural mechanism of blood clotting to evade the immune system. Normally, blood clotting is triggered in response to blood vessel damage; platelets begin to plug the clot, and a cascade of reactions occurs in which fibrinogen, a soluble protein made by the liver, is cleaved into fibrin. Fibrin is an insoluble, thread-like protein that binds to blood platelets, cross-links, and contracts to form a mesh of clumped platelets and red blood cells. The resulting clot prevents further loss of blood from the damaged blood vessels.

However, if bacteria release coagulase into the bloodstream, the fibrinogen-to-fibrin cascade is triggered in the absence of blood vessel damage. The resulting clot coats the bacteria in fibrin, protecting the bacteria from exposure to phagocytic immune cells circulating in the bloodstream.

Whereas coagulase causes blood to clot, kinases have the opposite effect by triggering the conversion of plasminogen to plasmin, which is involved in the digestion of fibrin clots. By digesting a clot, kinases allow pathogens trapped in the clot to escape and spread, similar to the way that collagenase, hyaluronidase, and DNAse facilitate the spread of infection. Examples of kinases include staphylokinases and streptokinases, produced by *Staphylococcus aureus* and *Streptococcus pyogenes*, respectively. It is intriguing that S. aureus can produce both coagulase to promote clotting and staphylokinase to stimulate the digestion of clots. The action of the coagulase provides an important protective barrier from the immune system, but when nutrient supplies are diminished or other conditions signal a need for the pathogen to escape and spread, the production of staphylokinase can initiate this process.

A final mechanism that pathogens can use to protect themselves against the immune system is called **antigenic variation**, which is the alteration of surface proteins so that a pathogen is no longer recognized by the host's immune system. For example, the bacterium *Borrelia burgdorferi*, the causative agent of Lyme disease, contains a surface lipoprotein known as VlsE. Because of genetic recombination during DNA replication and repair, this bacterial protein undergoes antigenic variation. Each time fever occurs, the VlsE protein in *B. burgdorferi* can differ so much that antibodies against previous VlsE sequences are not effective. It is believed that this variation in the VlsE contributes to the ability *B. burgdorferi* to cause chronic disease. Another important human bacterial pathogen that uses antigenic variation to avoid the immune system is *Neisseria gonorrhoeae*, which causes the sexually transmitted disease gonorrhea. This bacterium is well known for its ability to undergo antigenic variation of its type IV pili to avoid immune defenses.

### Exercise 3.3.2

- Name at least two ways that a capsule provides protection from the immune system.
- Besides capsules, name two other virulence factors used by bacteria to evade the immune system.

### Clinical Focus

**Resolution**

Based on Michael's reported symptoms of stiff neck and hemiparesis, the physician suspects that the infection may have spread to his nervous system. The physician decides to order a spinal tap to look for any bacteria that may have invaded the meninges and cerebrospinal fluid (CSF), which would normally be sterile. To perform the spinal tap, Michael's lower back is swabbed with an iodine antiseptic and then covered with a sterile sheet. The needle is aseptically removed from the manufacturer's sealed plastic packaging by the clinician's gloved hands. The needle is inserted and a small volume of fluid is drawn into an attached sample tube. The tube is removed, capped and a prepared label with Michael's data is affixed to it. This STAT (urgent or immediate analysis required) specimen is divided into three separate sterile tubes, each with 1 mL of CSF. These tubes are immediately taken to the hospital's lab, where they are analyzed in the clinical chemistry, hematology, and microbiology departments. The preliminary results from all three departments indicate there is a cerebrospinal infection occurring, with the microbiology department reporting the presence of a gram-positive rod in Michael's CSF.

These results confirm what his physician had suspected: Michael's new symptoms are the result of meningitis, acute inflammation of the membranes that protect the brain and spinal cord. Because meningitis can be life threatening and because the first antibiotic therapy was not effective in preventing the spread of infection, Michael is prescribed an aggressive course of two antibiotics, ampicillin and gentamicin, to be delivered intravenously. Michael remains in the hospital for several days for supportive care and for observation. After a week, he is allowed to return home for bed rest and oral antibiotics. After 3 weeks of this treatment, he makes a full recovery.

*Go back to the previous Clinical Focus box.*

## Viral Virulence

Although viral pathogens are not similar to bacterial pathogens in terms of structure, some of the properties that contribute to

their virulence are similar. Viruses use adhesins to facilitate adhesion to host cells, and certain enveloped viruses rely on antigenic variation to avoid the host immune defenses. These virulence factors are discussed in more detail in the following sections.

## Viral Adhesins

One of the first steps in any viral infection is adhesion of the virus to specific receptors on the surface of cells. This process is mediated by adhesins that are part of the viral capsid or membrane envelope. The interaction of viral adhesins with specific cell receptors defines the tropism (preferential targeting) of viruses for specific cells, tissues, and organs in the body. The spike protein hemagglutinin found on Influenzavirus is an example of a viral adhesin; it allows the virus to bind to the sialic acid on the membrane of host respiratory and intestinal cells. Another viral adhesin is the glycoprotein gp120, found on HIV. For HIV to infect cells of the immune system, it must interact with two receptors on the surface of cells. The first interaction involves binding between gp120 and the CD4 cellular marker that is found on some essential immune system cells. However, before viral entry into the cell can occur, a second interaction between gp120 and one of two chemokine receptors (CCR5 and CXCR4) must occur. ***Table*** 3.3.5 lists the adhesins for some common viral pathogens and the specific sites to which these adhesins allow viruses to attach.

*Table 3.3.5: Some Viral Adhesins and Their Host Attachment Sites*

| Pathogen | Disease | Adhesin | Attachment Site |
|---|---|---|---|
| Influenzavirus | Influenza | Hemagglutinin | Sialic acid of respiratory and intestinal cells |
| Herpes simplex virus I or II | Oral herpes, genital herpes | Glycoproteins gB, gC, gD | Heparan sulfate on mucosal surfaces of the mouth and genitals |
| Human immunodeficiency virus | HIV/AIDS | Glycoprotein gp120 | CD4 and CCR5 or CXCR4 of immune system cells |

## Antigenic Variation in Viruses

Antigenic variation also occurs in certain types of enveloped viruses, including influenza viruses, which exhibit two forms of antigenic variation: **antigenic drift** and **antigenic shift** (***Figure*** 3.3.9). Antigenic drift is the result of point mutations causing slight changes in the spike proteins hemagglutinin (H) and neuraminidase (N). On the other hand, antigenic shift is a major change in spike proteins due to gene reassortment. This reassortment for antigenic shift occurs typically when two different influenza viruses infect the same host.

The rate of antigenic variation in influenza viruses is very high, making it difficult for the immune system to recognize the many different strains of Influenzavirus. Although the body may develop immunity to one strain through natural exposure or vaccination, antigenic variation results in the continual emergence of new strains that the immune system will not recognize. This is the main reason that vaccines against Influenzavirus must be given annually. Each year's influenza vaccine provides protection against the most prevalent strains for that year, but new or different strains may be more prevalent the following year.

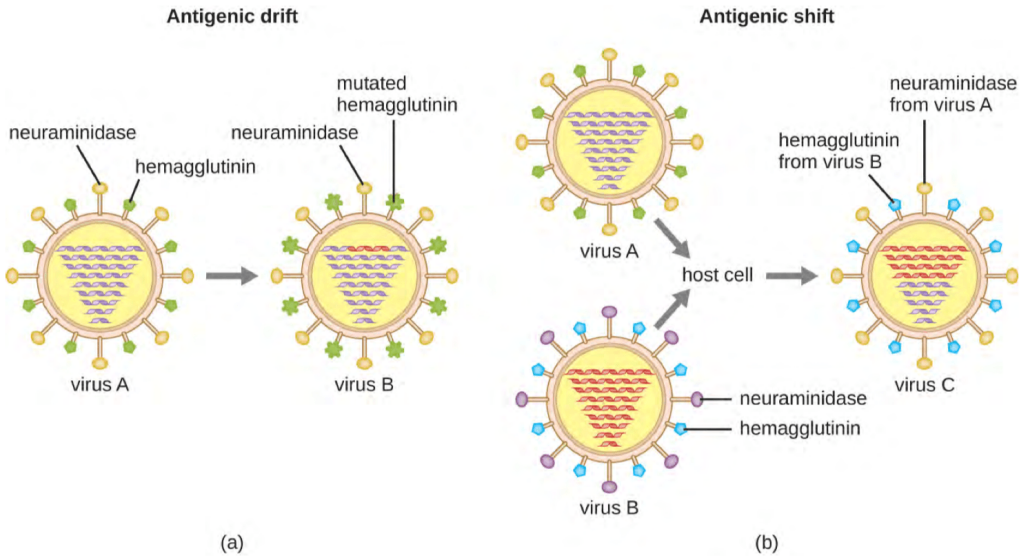



Figure 3.3.9: Antigenic drift and antigenic shift in influenza viruses. (a) In antigenic drift, mutations in the genes for the surface proteins neuraminidase and/or hemagglutinin result in small antigenic changes over time. (b) In antigenic shift, simultaneous infection of a cell with two different influenza viruses results in mixing of the genes. The resultant virus possesses a mixture of the proteins of the original viruses. Influenza pandemics can often be traced to antigenic shifts.

### Link to Learning

For another explanation of how **antigenic shift and drift** occur, watch this video.

### Exercise 3.3.3

- Describe the role of adhesins in viral tropism.
- Explain the difference between antigenic drift and antigenic shift.

## Key Concepts and Summary

- **Virulence factors** contribute to a pathogen's ability to cause disease.
- **Exoenzymes** and **toxins** allow pathogens to invade host tissue and cause tissue damage. Exoenzymes are classified according to the macromolecule they target and exotoxins are classified based on their mechanism of action.
- Bacterial toxins include **endotoxin** and **exotoxins**. Endotoxin is the lipid A component of the LPS of the gram- negative cell envelope. Exotoxins are proteins secreted mainly by gram-positive bacteria, but also are secreted by gram-negative bacteria.
- Bacterial pathogens may evade the host immune response by producing **capsules** to avoid phagocytosis, surviving the intracellular environment of phagocytes, degrading antibodies, or through **antigenic variation**.
- Viral pathogens use adhesins for initiating infections and antigenic variation to avoid immune defenses.
- Influenza viruses use both **antigenic drift** and **antigenic shift** to avoid being recognized by the immune system.

## Footnotes

1. V. Meka. "Panton-Valentine Leukocidin." http://www.antimicrobe.org/h04c.file...L-S-aureus.asp

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# 3.4: Virulence Factors of Eukaryotic Pathogens

**Learning Objectives**

- Describe virulence factors unique to fungi and parasites
- Compare virulence factors of fungi and bacteria
- Explain the difference between protozoan parasites and helminths
- Describe how helminths evade the host immune system

Although fungi and parasites are important pathogens causing infectious diseases, their pathogenic mechanisms and virulence factors are not as well characterized as those of bacteria. Despite the relative lack of detailed mechanisms, the stages of pathogenesis and general mechanisms of virulence involved in disease production by these pathogens are similar to those of bacteria.

## Fungal Virulence

Pathogenic fungi can produce virulence factors that are similar to the bacterial virulence factors that have been discussed earlier in this chapter. In this section, we will look at the virulence factors associated with species of *Candida*, *Cryptococcus*, *Claviceps*, and *Aspergillus*.

*Candida albicans* is an opportunistic fungal pathogen and causative agent of oral thrush, vaginal yeast infections, and cutaneous candidiasis. *Candida* produces adhesins (surface glycoproteins) that bind to the phospholipids of epithelial and endothelial cells. To assist in spread and tissue invasion, *Candida* produces proteases and phospholipases (i.e., exoenzymes). One of these proteases degrades keratin, a structural protein found on epithelial cells, enhancing the ability of the fungus to invade host tissue. In animal studies, it has been shown that the addition of a protease inhibitor led to attenuation of *Candida infection*.[1] Similarly, the phospholipases can affect the integrity of host cell membranes to facilitate invasion.

The main virulence factor for *Cryptococcus*, a fungus that causes pneumonia and meningitis, is capsule production. The polysaccharide glucuronoxylomannan is the principal constituent of the *Cryptococcus* capsule. Similar to encapsulated bacterial cells, encapsulated *Cryptococcus* cells are more resistant to phagocytosis than nonencapsulated *Cryptococcus*, which are effectively phagocytosed and, therefore, less virulent.

Like some bacteria, many fungi produce exotoxins. Fungal toxins are called **mycotoxins**. *Claviceps purpurea*, a fungus that grows on rye and related grains, produces a mycotoxin called ergot toxin, an alkaloid responsible for the disease known as ergotism. There are two forms of ergotism: gangrenous and convulsive. In gangrenous ergotism, the ergot toxin causes vasoconstriction, resulting in improper blood flow to the extremities, eventually leading to gangrene. A famous outbreak of gangrenous ergotism occurred in Eastern Europe during the 5th century AD due to the consumption of rye contaminated with *C. purpurea*. In convulsive ergotism, the toxin targets the central nervous system, causing mania and hallucinations.

The mycotoxin aflatoxin is a virulence factor produced by the fungus Aspergillus, an opportunistic pathogen that can enter the body via contaminated food or by inhalation. Inhalation of the fungus can lead to the chronic pulmonary disease aspergillosis, characterized by fever, bloody sputum, and/or asthma. Aflatoxin acts in the host as both a mutagen (a substance that causes mutations in DNA) and a **carcinogen** (a substance involved in causing cancer), and has been associated with the development of liver cancer. Aflatoxin has also been shown to cross the blood-placental barrier.[2] A second mycotoxin produced by *Aspergillus* is gliotoxin. This toxin promotes virulence by inducing host cells to self-destruct and by evading the host's immune response by inhibiting the function of phagocytic cells as well as the pro-inflammatory response. Like *Candida*, *Aspergillus* also produces several proteases. One is elastase, which breaks down the protein elastin found in the connective tissue of the lung, leading to the development of lung disease. Another is catalase, an enzyme that protects the fungus from hydrogen peroxide produced by the immune system to destroy pathogens.

**Exercise 3.4.1**

- Explain how antigenic variation by protozoan pathogens helps them survive in the host.

## Helminth Virulence

Helminths, or parasitic worms, are multicellular eukaryotic parasites that depend heavily on virulence factors that allow them to gain entry to host tissues. For example, the aquatic larval form of *Schistosoma mansoni*, which causes schistosomiasis, penetrates intact skin with the aid of proteases that degrade skin proteins, including elastin.

To survive within the host long enough to perpetuate their often-complex life cycles, helminths need to evade the immune system. Some helminths are so large that the immune system is ineffective against them. Others, such as adult roundworms (which cause trichinosis, ascariasis, and other diseases), are protected by a tough outer cuticle.

Over the course of their life cycles, the surface characteristics of the parasites vary, which may help prevent an effective immune response. Some helminths express polysaccharides called glycans on their external surface; because these glycans resemble molecules produced by host cells, the immune system fails to recognize and attack the helminth as a foreign body. This "glycan gimmickry," as it has been called, serves as a protective cloak that allows the helminth to escape detection by the immune system. [3]

In addition to evading host defenses, helminths can actively suppress the immune system. *S. mansoni*, for example, degrades host antibodies with proteases. Helminths produce many other substances that suppress elements of both innate nonspecific and adaptive specific host defenses. They also release large amounts of material into the host that may locally overwhelm the immune system or cause it to respond inappropriately.

**Exercise 3.4.2**

- Describe how helminths avoid being destroyed by the host immune system.

## Key Concepts and Summary

- Fungal and parasitic pathogens use pathogenic mechanisms and virulence factors that are similar to those of bacterial pathogens
- Fungi initiate infections through the interaction of adhesins with receptors on host cells. Some fungi produce toxins and exoenzymes involved in disease production and capsules that provide protection of phagocytosis.
- Protozoa adhere to target cells through complex mechanisms and can cause cellular damage through release of cytopathic substances. Some protozoa avoid the immune system through antigenic variation and production of capsules.
- Helminthic worms are able to avoid the immune system by coating their exteriors with glycan molecules that make them look like host cells or by suppressing the immune system.

## Footnotes

1. K. Fallon et al. "Role of Aspartic Proteases in Disseminated *Candida albicans* Infection in Mice." *Infection* and *Immunity* 65 no. 2 (1997):551–556.
2. C.P. Wild et al. "In-utero exposure to aflatoxin in west Africa." *Lancet* 337 no. 8757 (1991):1602.
3. I. van Die, R.D. Cummings. "Glycan Gimmickry by Parasitic Helminths: A Strategy for Modulating the Host Immune Response?" *Glycobiology* 20 no. 1 (2010):2–12.

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# 3.5: Review Questions

## Multiple Choice

1. Which of the following would be a sign of an infection?
   A. muscle aches
   B. headache
   C. fever
   D. nausea

*Answer available at the end of this section.*

2. Which of the following is an example of a noncommunicable infectious disease?
   A. infection with a respiratory virus
   B. food poisoning due to a preformed bacterial toxin in food
   C. skin infection acquired from a dog bite
   D. infection acquired from the stick of a contaminated needle

*Answer available at the end of this section.*

3. During an oral surgery, the surgeon nicked the patient's gum with a sharp instrument. This allowed *Streptococcus*, a bacterium normally present in the mouth, to gain access to the blood. As a result, the patient developed bacterial endocarditis (an infection of the heart). Which type of disease is this?
   A. iatrogenic
   B. nosocomial
   C. vectors
   D. zoonotic

*Answer available at the end of this section.*

4. Which period is the stage of disease during which the patient begins to present general signs and symptoms?
   A. convalescence
   B. incubation
   C. illness
   D. prodromal

*Answer available at the end of this section.*

5. A communicable disease that can be easily transmitted from person to person is which type of disease?
   A. contagious
   B. iatrogenic
   C. acute
   D. nosocomial

*Answer available at the end of this section.*

6. Which of the following is a pathogen that could not be identified by the original Koch's postulates?
   A. *Staphylococcus aureus*
   B. *Pseudomonas aeruginosa*
   C. Human immunodeficiency virus
   D. *Salmonella enterica* serovar Typhimurium

*Answer available at the end of this section.*

7. Pathogen A has an $ID_{50}$ of 50 particles, pathogen B has an $ID_{50}$ of 1,000 particles, and pathogen C has an $ID_{50}$ of 1 × 106 particles. Which pathogen is most virulent?
   A. pathogen A
   B. pathogen B
   C. pathogen C

*Answer available at the end of this section.*

8. Which of the following choices lists the steps of pathogenesis in the correct order?
   A. invasion, infection, adhesion, exposure
   B. adhesion, exposure, infection, invasion
   C. exposure, adhesion, invasion, infection
   D. disease, infection, exposure, invasion

*Answer available at the end of this section.*

9. Which of the following would be a virulence factor of a pathogen?
   A. a surface protein allowing the pathogen to bind to host cells
   B. a secondary host the pathogen can infect
   C. a surface protein the host immune system recognizes
   D. the ability to form a provirus

*Answer available at the end of this section.*

10. You have recently identified a new toxin. It is produced by a gram-negative bacterium. It is composed mostly of protein, has high toxicity, and is not heat stable. You also discover that it targets liver cells. Based on these characteristics, how would you classify this toxin?
    A. superantigen
    B. endotoxin
    C. exotoxin
    D. leukocidin

*Answer available at the end of this section.*

11. Which of the following applies to hyaluronidase?
    A. It acts as a spreading factor.
    B. It promotes blood clotting.
    C. It is an example of an adhesin.
    D. It is produced by immune cells to target pathogens.

*Answer available at the end of this section.*

12. Phospholipases are enzymes that do which of the following?
    A. degrade antibodies
    B. promote pathogen spread through connective tissue.
    C. degrade nucleic acid to promote spread of pathogen
    D. degrade cell membranes to allow pathogens to escape phagosomes

*Answer available at the end of this section.*

13. Which of the following is a major virulence factor for the fungal pathogen *Cryptococcus*?
    A. hemolysin
    B. capsule
    C. collagenase
    D. fimbriae

*Answer available at the end of this section.*

14. Which of the following pathogens undergoes antigenic variation to avoid immune defenses?

A. *Candida*
B. *Cryptococcus*
C. *Plasmodium*
D. *Giardia*

*Answer available at the end of this section.*

## Fill in the Blank

15. A difference between an acute disease and chronic disease is that chronic diseases have an extended period of _____.

*Answer available at the end of this section.*

16. A person steps on a rusty nail and develops tetanus. In this case, the person has acquired a(n) _____ disease.

*Answer available at the end of this section.*

17. A(n) _____ pathogen causes disease only when conditions are favorable for the microorganism because of transfer to an inappropriate body site or weakened immunity in an individual.

*Answer available at the end of this section.*

18. The concentration of pathogen needed to kill 50% of an infected group of test animals is the _____.

*Answer available at the end of this section.*

19. A(n) _____ infection is a small region of infection from which a pathogen may move to another part of the body to establish a second infection.

*Answer available at the end of this section.*

20. Cilia, fimbriae, and pili are all examples of structures used by microbes for _____.

*Answer available at the end of this section.*

21. The glycoprotein adhesion gp120 on HIV must interact with _____ on some immune cells as the first step in the process of infecting the cell.

*Answer available at the end of this section.*

22. Adhesins are usually located on _____ of the pathogen and are composed mainly of _____ and _____.

*Answer available at the end of this section.*

23. The Shiga and diphtheria toxins target _____ in host cells.

*Answer available at the end of this section.*

24. Antigenic _____ is the result of reassortment of genes responsible for the production of influenza virus spike proteins between different virus particles while in the same host, whereas antigenic _____ is the result of point mutations in the spike proteins.

*Answer available at the end of this section.*

25. *Candida* can invade tissue by producing the exoenzymes _____ and _____.

*Answer available at the end of this section.*

26. The larval form of *Schistosoma mansoni* uses a _____ to help it gain entry through intact skin.

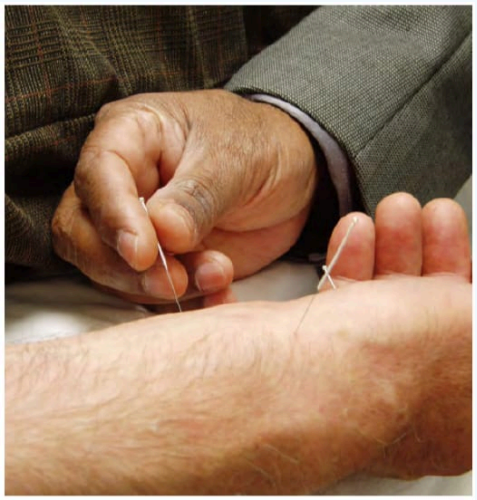
*Answer available at the end of this section.*

## Short Answer

27. Brian goes to the hospital after not feeling well for a week. He has a fever of 38 °C (100.4 °F) and complains of nausea and a constant migraine. Distinguish between the signs and symptoms of disease in Brian's case.
28. Describe the virulence factors associated with the fungal pathogen *Aspergillus*.
29. Explain how helminths evade the immune system.

## Critical Thinking

30. Two periods of acute disease are the periods of illness and period of decline. (a) In what way are both of these periods similar? (b) In terms of quantity of pathogen, in what way are these periods different? (c) What initiates the period of decline?
31. In July 2015, a report[1] was released indicating the gram-negative bacterium Pseudomonas aeruginosa was found on hospital sinks 10 years after the initial outbreak in a neonatal intensive care unit. *P. aeruginosa* usually causes localized ear and eye infections but can cause pneumonia or septicemia in vulnerable individuals like newborn babies. Explain how the current discovery of the presence of this reported *P. aeruginosa* could lead to a recurrence of nosocomial disease.
32. Diseases that involve biofilm-producing bacteria are of serious concern. They are not as easily treated compared with those involving free-floating (or planktonic) bacteria. Explain three reasons why biofilm formers are more pathogenic.
33. A microbiologist has identified a new gram-negative pathogen that causes liver disease in rats. She suspects that the bacterium's fimbriae are a virulence factor. Describe how molecular Koch's postulates could be used to test this hypothesis.
34. Acupuncture is a form of alternative medicine that is used for pain relief. Explain how acupuncture could facilitate exposure to pathogens



35. Two types of toxins are hemolysins and leukocidins. (a) How are these toxins similar? (b) How do they differ?
36. Imagine that a mutation in the gene encoding the cholera toxin was made. This mutation affects the A-subunit, preventing it from interacting with any host protein. (a) Would the toxin be able to enter into the intestinal epithelial cell? (b) Would the toxin be able to cause diarrhea?

# Footnotes

1. C. Owens. "*P. aeruginosa* survives in sinks 10 years after hospital outbreak." 2015. http://www.healio.com/infectious-disease/nosocomial-infections/news/online/%7B5afba909-56d9-48cc-a9b0-ffe4568161e8%7D/p-aeruginosa-survives-in-

## Answers

**Multiple Choice**
C

**Multiple Choice**
B

**Multiple Choice**
A

**Multiple Choice**
D

**Multiple Choice**
A

**Multiple Choice**
C

**Multiple Choice**
A

**Multiple Choice**
C

**Multiple Choice**
A

**Multiple Choice**
C

**Multiple Choice**
A

**Multiple Choice**
D

**Multiple Choice**
B

**Multiple Choice**
C

**Fill in the Blank**
illness

**Fill in the Blank**
noncommunicable

**Fill in the Blank**
opportunistic

**Fill in the Blank**
$LD_{50}$

**Fill in the Blank**
focal

**Fill in the Blank**
adhesion

**Fill in the Blank**
CD4

**Fill in the Blank**
surface; proteins; sugars

**Fill in the Blank**
protein synthesis

**Fill in the Blank**
shift; drift

**Fill in the Blank**
protease and phospholipase

**Fill in the Blank**
protease

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# 3: MICROBIAL MECHANISMS OF PATHOGENICITY

Jane woke up one spring morning feeling not quite herself. Her throat felt a bit dry and she was sniffling. She wondered why she felt so lousy. Was it because of a change in the weather? The pollen count? Was she coming down with something? Did she catch a bug from her coworker who sneezed on her in the elevator yesterday?

The signs and symptoms we associate with illness can have many different causes. Sometimes they are the direct result of a pathogenic infection, but in other cases they result from a response by our immune system to a pathogen or another perceived threat. For example, in response to certain pathogens, the immune system may release pyrogens, chemicals that cause the body temperature to rise, resulting in a fever. This response creates a less-than-favorable environment for the pathogen, but it also makes us feel sick.

Medical professionals rely heavily on analysis of signs and symptoms to determine the cause of an ailment and prescribe treatment. In some cases, signs and symptoms alone are enough to correctly identify the causative agent of a disease, but since few diseases produce truly unique symptoms, it is often necessary to confirm the identity of the infectious agent by other direct and indirect diagnostic methods.

## Chapter Outline


3.1: Characteristics of Infectious Disease

3.2: How Pathogens Cause Disease

3.3: Virulence Factors of Bacterial and Viral Pathogens

3.4: Virulence Factors of Eukaryotic Pathogens

3.5: Review Questions



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# WEEK 4


## 4: Innate Nonspecific Host Defenses

4.1: Physical Defenses

4.2: Chemical Defenses

4.3: Cellular Defenses

4.4: Pathogen Recognition and Phagocytosis

4.5: Inflammation and Fever

4.6: Review Questions

## 5: Adaptive Specific Host Defenses

5.1: Overview of Specific Adaptive Immunity

5.2: Major Histocompatibility Complexes and Antigen- Presenting Cells

5.3: T Lymphocytes and Cellular Immunity

5.4: B Lymphocytes and Humoral Immunity

5.5: Vaccines

5.6: Review Questions

## 6: Immune System, Part 1 (Video)

## 7: Immune System, Part 2 (Video)

## 8: Immune System, Part 3 (Video)


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# 4: INNATE NONSPECIFIC HOST DEFENSES

Despite relatively constant exposure to pathogenic microbes in the environment, humans do not generally suffer from constant infection or disease. Under most circumstances, the body is able to defend itself from the threat of infection thanks to a complex immune system designed to repel, kill, and expel disease-causing invaders. Immunity as a whole can be described as two interrelated parts: nonspecific innate immunity, which is the subject of this chapter, and specific adaptive host defenses, which are discussed in the next chapter.

The nonspecific innate immune response provides a first line of defense that can often prevent infections from gaining a solid foothold in the body. These defenses are described as *nonspecific* because they do not target any specific pathogen; rather, they defend against a wide range of potential pathogens. They are called *innate* because they are built-in mechanisms of the human organism. Unlike the specific adaptive defenses, they are not acquired over time and they have no “memory” (they do not improve after repeated exposures to specific pathogens).

Broadly speaking, nonspecific innate defenses provide an immediate (or very rapid) response against potential pathogens. However, these responses are neither perfect nor impenetrable. They can be circumvented by pathogens on occasion, and sometimes they can even cause damage to the body, contributing to the signs and symptoms of infection (***Figure on Thumbnail***)

## Chapter Outline


4.1: Physical Defenses

4.2: Chemical Defenses

4.3: Cellular Defenses

4.4: Pathogen Recognition and Phagocytosis

4.5: Inflammation and Fever

4.6: Review Questions


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# 4.1: Physical Defenses

## Learning Objectives

- Describe the various physical barriers and mechanical defenses that protect the human body against infection and disease
- Describe the role of microbiota as a first-line defense against infection and disease

Nonspecific innate immunity can be characterized as a multifaceted system of defenses that targets invading pathogens in a nonspecific manner. In this chapter, we have divided the numerous defenses that make up this system into three categories: physical defenses, chemical defenses, and cellular defenses. However, it is important to keep in mind that these defenses do not function independently, and the categories often overlap. ***Table*** 4.1.1 provides an overview of the nonspecific defenses discussed in this chapter.

*Table* 4.1.1*: Overview of Nonspecific Innate Immune Defenses*

| | |
|---|---|
| Physical defenses | Physical barriers |
| | Mechanical defenses |
| | Microbiome |
| Chemical defenses | Chemicals and enzymes in body fluids |
| | Antimicrobial peptides |
| | Plasma protein mediators |
| | Cytokines |
| | Inflammation-eliciting mediators |
| Cellular defenses | Granulocytes |
| | Agranulocytes |

## Clinical Focus

**Part 1**

Angela, a 25-year-old female patient in the emergency department, is having some trouble communicating verbally because of shortness of breath. A nurse observes constriction and swelling of the airway and labored breathing. The nurse asks Angela if she has a history of asthma or allergies. Angela shakes her head no, but there is fear in her eyes. With some difficulty, she explains that her father died suddenly at age 27, when she was just a little girl, of a similar respiratory attack. The underlying cause had never been identified.

- What are some possible causes of constriction and swelling of the airway?
- What causes swelling of body tissues in general?

*Jump to the next Clinical Focus box.*

Physical defenses provide the body's most basic form of nonspecific defense. They include physical barriers to microbes, such as the skin and mucous membranes, as well as mechanical defenses that physically remove microbes and debris from areas of the body where they might cause harm or infection. In addition, the microbiome provides a measure of physical protection against disease, as microbes of the normal microbiota compete with pathogens for nutrients and cellular binding sites necessary to cause infection.

# Physical Barriers

Physical barriers play an important role in preventing microbes from reaching tissues that are susceptible to infection. At the cellular level, barriers consist of cells that are tightly joined to prevent invaders from crossing through to deeper tissue. For example, the endothelial cells that line blood vessels have very tight cell-to-cell junctions, blocking microbes from gaining access to the bloodstream. Cell junctions are generally composed of cell membrane proteins that may connect with the extracellular matrix or with complementary proteins from neighboring cells. Tissues in various parts of the body have different types of cell junctions. These include tight junctions, desmosomes, and gap junctions, as illustrated in ***Figure*** 4.1.1. Invading microorganisms may attempt to break down these substances chemically, using enzymes such as proteases that can cause structural damage to create a point of entry for pathogens.

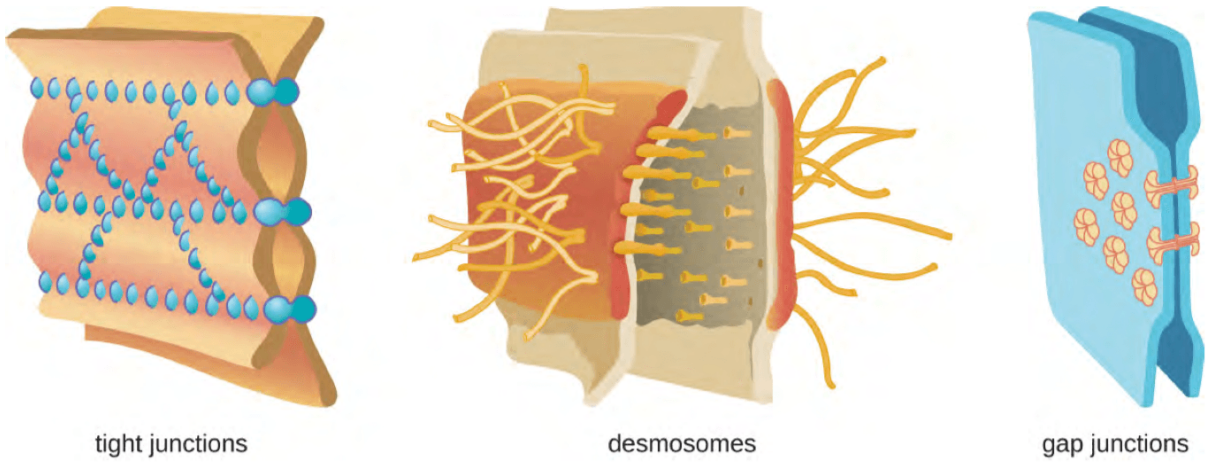



Figure 4.1.1: There are multiple types of cell junctions in human tissue, three of which are shown here. Tight junctions rivet two adjacent cells together, preventing or limiting material exchange through the spaces between them. Desmosomes have intermediate fibers that act like shoelaces, tying two cells together, allowing small materials to pass through the resulting spaces. Gap junctions are channels between two cells that permit their communication via signals. (credit: modification of work by Mariana Ruiz Villareal)

## The Skin Barrier

One of the body's most important physical barriers is the skin barrier, which is composed of three layers of closely packed cells. The thin upper layer is called the epidermis. A second, thicker layer, called the dermis, contains hair follicles, sweat glands, nerves, and blood vessels. A layer of fatty tissue called the hypodermis lies beneath the dermis and contains blood and lymph vessels (***Figure*** 4.1.2).

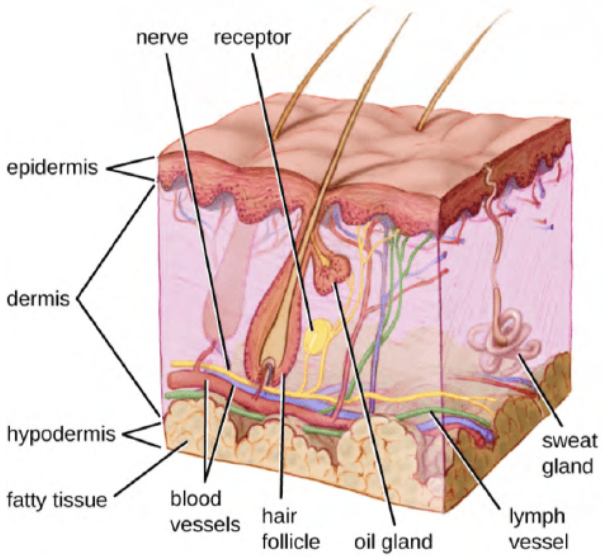



Figure 4.1.2: Human skin has three layers, the epidermis, the dermis, and the hypodermis, which provide a thick barrier between microbes outside the body and deeper tissues. Dead skin cells on the surface of the epidermis are continually shed, taking with them microbes on the skin's surface. (credit: modification of work by National Institutes of Health)

The topmost layer of skin, the epidermis, consists of cells that are packed with keratin. These dead cells remain as a tightly connected, dense layer of protein-filled cell husks on the surface of the skin. The keratin makes the skin's surface mechanically tough and resistant to degradation by bacterial enzymes. Fatty acids on the skin's surface create a dry, salty, and acidic environment that inhibits the growth of some microbes and is highly resistant to breakdown by bacterial enzymes. In addition, the dead cells of the epidermis are frequently shed, along with any microbes that may be clinging to them. Shed skin cells are continually replaced with new cells from below, providing a new barrier that will soon be shed in the same way.

Infections can occur when the skin barrier is compromised or broken. A wound can serve as a point of entry for opportunistic pathogens, which can infect the skin tissue surrounding the wound and possibly spread to deeper tissues.

## Case in Point

**Every Rose Has its Thorn**

Mike, a gardener from southern California, recently noticed a small red bump on his left forearm. Initially, he did not think much of it, but soon it grew larger and then ulcerated (opened up), becoming a painful lesion that extended across a large part of his forearm (***Figure*** 4.1.3). He went to an urgent care facility, where a physician asked about his occupation. When he said he was a landscaper, the physician immediately suspected a case of sporotrichosis, a type of fungal infection known as rose gardener's disease because it often afflicts landscapers and gardening enthusiasts.

Under most conditions, fungi cannot produce skin infections in healthy individuals. Fungi grow filaments known as hyphae, which are not particularly invasive and can be easily kept at bay by the physical barriers of the skin and mucous membranes. However, small wounds in the skin, such as those caused by thorns, can provide an opening for opportunistic pathogens like *Sporothrix schenkii*, a soil-dwelling fungus and the causative agent of rose gardener's disease. Once it breaches the skin barrier, S. *schenkii* can infect the skin and underlying tissues, producing ulcerated lesions like Mike's. Compounding matters, other pathogens may enter the infected tissue, causing secondary bacterial infections.

Luckily, rose gardener's disease is treatable. Mike's physician wrote him a prescription for some antifungal drugs as well as a course of antibiotics to combat secondary bacterial infections. His lesions eventually healed, and Mike returned to work with a new appreciation for gloves and protective clothing.



Figure 4.1.3: Rose gardener's disease can occur when the fungus *Sporothrix schenkii* breaches the skin through small cuts, such as might be inflicted by thorns. (credit left: modification of work by Elisa Self; credit right: modification of work by Centers for Disease Control and Prevention)

## Mucous Membranes

The **mucous membranes** lining the nose, mouth, lungs, and urinary and digestive tracts provide another nonspecific barrier against potential pathogens. Mucous membranes consist of a layer of epithelial cells bound by tight junctions. The epithelial cells secrete a moist, sticky substance called **mucus**, which covers and protects the more fragile cell layers beneath it and traps debris and particulate matter, including microbes. Mucus secretions also contain antimicrobial peptides.

In many regions of the body, mechanical actions serve to flush mucus (along with trapped or dead microbes) out of the body or away from potential sites of infection. For example, in the respiratory system, inhalation can bring microbes, dust, mold spores, and other small airborne debris into the body. This debris becomes trapped in the mucus lining the respiratory tract, a layer known as the mucociliary blanket. The epithelial cells lining the upper parts of the respiratory tract are called **ciliated epithelial cells** because they have hair-like appendages known as cilia. Movement of the cilia propels debris-laden mucus out and away from the lungs. The expelled mucus is then swallowed and destroyed in the stomach, or coughed up, or sneezed out (***Figure*** 4.1.4). This system of removal is often called the **mucociliary escalator**.

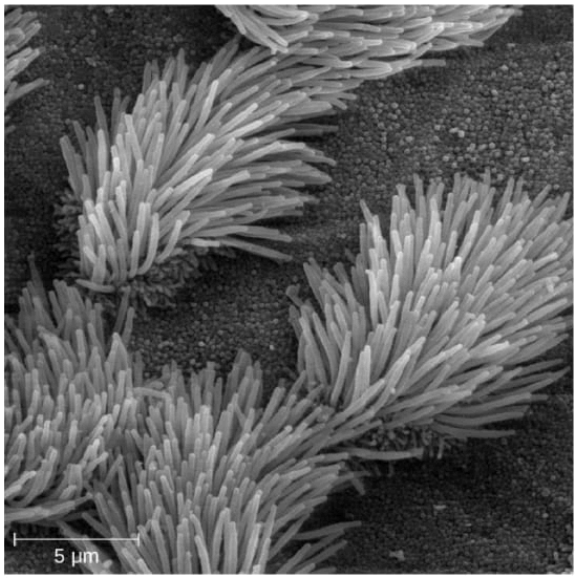



Figure 4.1.4: This scanning electron micrograph shows ciliated and nonciliated epithelial cells from the human trachea. The mucociliary escalator pushes mucus away from the lungs, along with any debris or microorganisms that may be trapped in the sticky mucus, and the mucus moves up to the esophagus where it can be removed by swallowing.

The mucociliary escalator is such an effective barrier to microbes that the lungs, the lowermost (and most sensitive) portion of the respiratory tract, were long considered to be a sterile environment in healthy individuals. Only recently has research

suggested that healthy lungs may have a small normal microbiota. Disruption of the mucociliary escalator by the damaging effects of smoking or diseases such as cystic fibrosis can lead to increased colonization of bacteria in the lower respiratory tract and frequent infections, which highlights the importance of this physical barrier to host defenses.

Like the respiratory tract, the digestive tract is a portal of entry through which microbes enter the body, and the mucous membranes lining the digestive tract provide a nonspecific physical barrier against ingested microbes. The intestinal tract is lined with epithelial cells, interspersed with mucus-secreting goblet cells (***Figure*** 4.1.5). This mucus mixes with material received from the stomach, trapping foodborne microbes and debris. The mechanical action of **peristalsis**, a series of muscular contractions in the digestive tract, moves the sloughed mucus and other material through the intestines, rectum, and anus, excreting the material in feces.

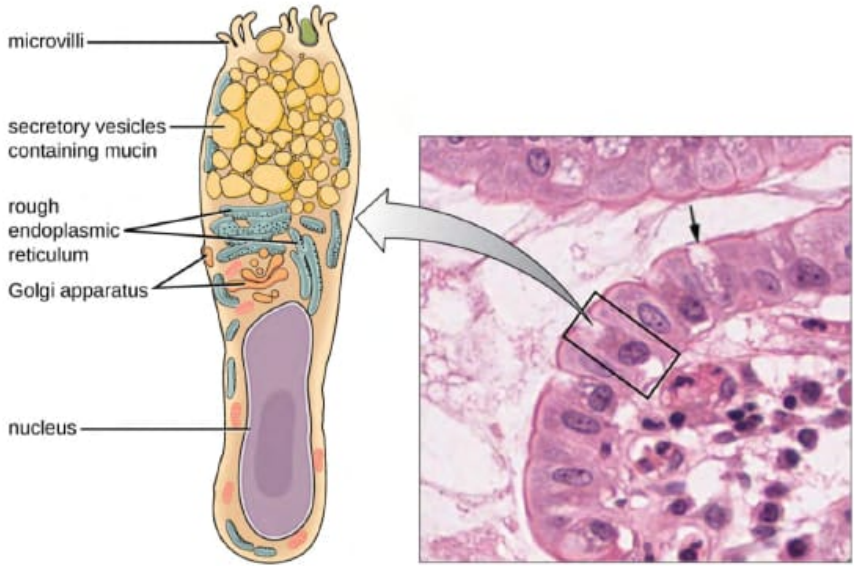



Figure 4.1.5: Goblet cells produce and secrete mucus. The arrows in this micrograph point to the mucus-secreting goblet cells (magnification 1600×) in the intestinal epithelium. (credit micrograph: Micrograph provided by the Regents of University of Michigan Medical School © 2012)

## Endothelia

The epithelial cells lining the urogenital tract, blood vessels, lymphatic vessels, and certain other tissues are known as **endothelia**. These tightly packed cells provide a particularly effective frontline barrier against invaders. The endothelia of the **blood-brain barrier**, for example, protect the central nervous system (CNS), which consists of the brain and the spinal cord. The CNS is one of the most sensitive and important areas of the body, as microbial infection of the CNS can quickly lead to serious and often fatal inflammation. The cell junctions in the blood vessels traveling through the CNS are some of the tightest and toughest in the body, preventing any transient microbes in the bloodstream from entering the CNS. This keeps the cerebrospinal fluid that surrounds and bathes the brain and spinal cord sterile under normal conditions.

### Exercise 4.1.1

- Describe how the mucociliary escalator functions.
- Name two places you would find endothelia.

# Mechanical Defenses

In addition to physical barriers that keep microbes out, the body has a number of mechanical defenses that physically remove pathogens from the body, preventing them from taking up residence. We have already discussed several examples of mechanical defenses, including the shedding of skin cells, the expulsion of mucus via the mucociliary escalator, and the excretion of feces through intestinal peristalsis. Other important examples of mechanical defenses include the flushing action of urine and tears, which both serve to carry microbes away from the body. The flushing action of urine is largely responsible for the normally sterile environment of the urinary tract, which includes the kidneys, ureters, and urinary bladder. Urine passing out of the body washes

out transient microorganisms, preventing them from taking up residence. The eyes also have physical barriers and mechanical mechanisms for preventing infections. The eyelashes and eyelids prevent dust and airborne microorganisms from reaching the surface of the eye. Any microbes or debris that make it past these physical barriers may be flushed out by the mechanical action of blinking, which bathes the eye in tears, washing debris away (***Figure*** 4.1.6).

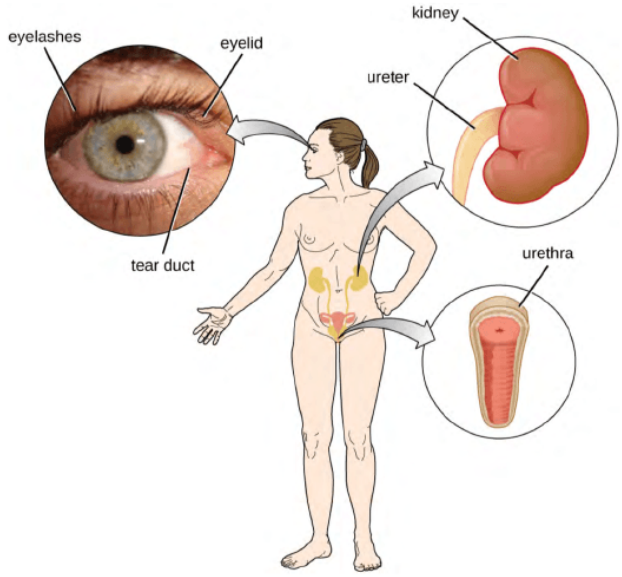



Figure 4.1.6: Tears flush microbes away from the surface of the eye. Urine washes microbes out of the urinary tract as it passes through; as a result, the urinary system is normally sterile.

**Exercise 4.1.2**

- Name two mechanical defenses that protect the eyes.

## Microbiome

In various regions of the body, resident microbiota serve as an important first-line defense against invading pathogens. Through their occupation of cellular binding sites and competition for available nutrients, the resident microbiota prevent the critical early steps of pathogen attachment and proliferation required for the establishment of an infection. For example, in the vagina, members of the resident microbiota compete with opportunistic pathogens like the yeast *Candida*. This competition prevents infections by limiting the availability of nutrients, thus inhibiting the growth of *Candida*, keeping its population in check. Similar competitions occur between the microbiota and potential pathogens on the skin, in the upper respiratory tract, and in the gastrointestinal tract. As will be discussed later in this chapter, the resident microbiota also contribute to the chemical defenses of the innate nonspecific host defenses. The importance of the normal microbiota in host defenses is highlighted by the increased susceptibility to infectious diseases when the microbiota is disrupted or eliminated. Treatment with antibiotics can significantly deplete the normal microbiota of the gastrointestinal tract, providing an advantage for pathogenic bacteria to colonize and cause diarrheal infection. In the case of diarrhea caused by *Clostridium difficile*, the infection can be severe and potentially lethal. One strategy for treating *C. difficile* infections is fecal transplantation, which involves the transfer of fecal material from a donor (screened for potential pathogens) into the intestines of the recipient patient as a method of restoring the normal microbiota and combating *C. difficile* infections.

***Table*** 4.1.2 provides a summary of the physical defenses discussed in this section.

*Table 4.1.2: Physical Defenses of Nonspecific Innate Immunity*

| Defense | Examples | Function |
|---|---|---|
| Cellular barriers | Skin, mucous membranes, endothelial cells | Deny entry to pathogens |

| Defense | Examples | Function |
|---|---|---|
| Mechanical defenses | Shedding of skin cells, mucociliary sweeping, peristalsis, flushing action of urine and tears | Remove pathogens from potential sites of infection |
| Microbiome | Resident bacteria of the skin, upper respiratory tract, gastrointestinal tract, and genitourinary tract | Compete with pathogens for cellular binding sites and nutrients |

### Exercise 4.1.3

- List two ways resident microbiota defend against pathogens.

## Key Concepts and Summary

- **Nonspecific innate immunity** provides a first line of defense against infection by nonspecifically blocking entry of microbes and targeting them for destruction or removal from the body.
- The physical defenses of innate immunity include physical barriers, mechanical actions that remove microbes and debris, and the microbiome, which competes with and inhibits the growth of pathogens.
- The skin, mucous membranes, and endothelia throughout the body serve as physical barriers that prevent microbes from reaching potential sites of infection. Tight cell junctions in these tissues prevent microbes from passing through.
- Microbes trapped in dead skin cells or **mucus** are removed from the body by mechanical actions such as shedding of skin cells, mucociliary sweeping, coughing, **peristalsis**, and flushing of bodily fluids (e.g., urination, tears)
- The resident microbiota provide a physical defense by occupying available cellular binding sites and competing with pathogens for available nutrients.

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# 4.2: Chemical Defenses

**Learning Objectives**

- Describe how enzymes in body fluids provide protection against infection or disease
- List and describe the function of antimicrobial peptides, complement components, cytokines, and acute-phase proteins
- Describe similarities and differences among classic, alternate, and lectin complement pathways

In addition to physical defenses, the innate nonspecific immune system uses a number of **chemical mediators** that inhibit microbial invaders. The term "chemical mediators" encompasses a wide array of substances found in various body fluids and tissues throughout the body. Chemical mediators may work alone or in conjunction with each other to inhibit microbial colonization and infection.

Some chemical mediators are endogenously produced, meaning they are produced by human body cells; others are produced exogenously, meaning that they are produced by certain microbes that are part of the microbiome. Some mediators are produced continually, bathing the area in the antimicrobial substance; others are produced or activated primarily in response to some stimulus, such as the presence of microbes.

## Chemical and Enzymatic Mediators Found in Body Fluids

Fluids produced by the skin include examples of both endogenous and exogenous mediators. Sebaceous glands in the dermis secrete an oil called sebum that is released onto the skin surface through hair follicles. This sebum is an endogenous mediator, providing an additional layer of defense by helping seal off the pore of the hair follicle, preventing bacteria on the skin's surface from invading sweat glands and surrounding tissue (***Figure*** 4.2.1). Certain members of the microbiome, such as the bacterium Propionibacterium acnes and the fungus Malassezia, among others, can use lipase enzymes to degrade sebum, using it as a food source. This produces oleic acid, which creates a mildly acidic environment on the surface of the skin that is inhospitable to many pathogenic microbes. Oleic acid is an example of an exogenously produced mediator because it is produced by resident microbes and not directly by body cells.

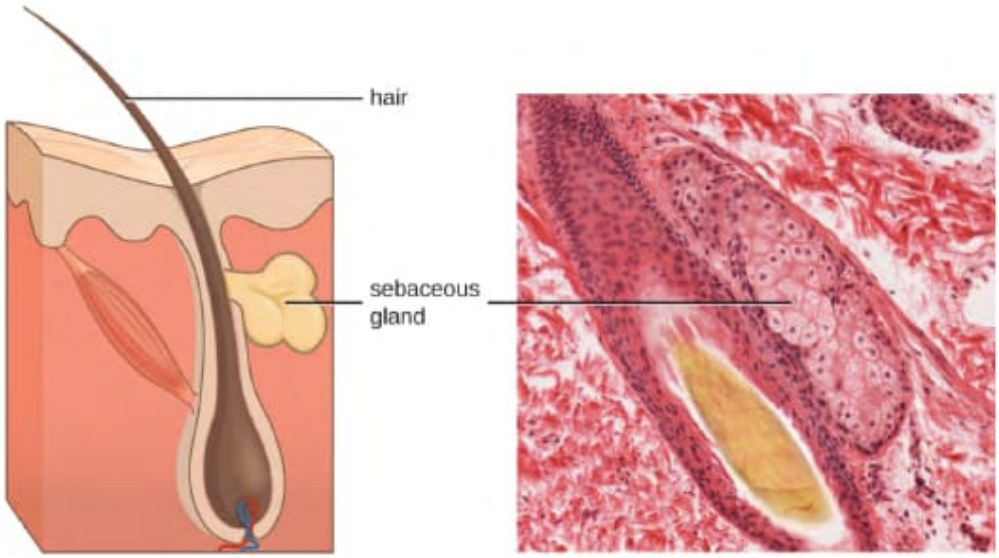



Figure 4.2.1: Sebaceous glands secrete sebum, a chemical mediator that lubricates and protect the skin from invading microbes. Sebum is also a food source for resident microbes that produce oleic acid, an exogenously produced mediator. (credit micrograph: Micrograph provided by the Regents of University of Michigan Medical School © 2012)

Environmental factors that affect the microbiota of the skin can have a direct impact on the production of chemical mediators. Low humidity or decreased sebum production, for example, could make the skin less habitable for microbes that produce oleic

acid, thus making the skin more susceptible to pathogens normally inhibited by the skin's low pH. Many skin moisturizers are formulated to counter such effects by restoring moisture and essential oils to the skin.

The digestive tract also produces a large number of chemical mediators that inhibit or kill microbes. In the oral cavity, saliva contains mediators such as lactoperoxidase enzymes, and mucus secreted by the esophagus contains the antibacterial enzyme lysozyme. In the stomach, highly acidic gastric fluid kills most microbes. In the lower digestive tract, the intestines have pancreatic and intestinal enzymes, antibacterial peptides (cryptins), bile produced from the liver, and specialized Paneth cells that produce lysozyme. Together, these mediators are able to eliminate most pathogens that manage to survive the acidic environment of the stomach.

In the urinary tract, urine flushes microbes out of the body during urination. Furthermore, the slight acidity of urine (the average pH is about 6) inhibits the growth of many microbes and potential pathogens in the urinary tract.

The female reproductive system employs lactate, an exogenously produced chemical mediator, to inhibit microbial growth. The cells and tissue layers composing the vagina produce glycogen, a branched and more complex polymer of glucose. Lactobacilli in the area ferment glycogen to produce lactate, lowering the pH in the vagina and inhibiting transient microbiota, opportunistic pathogens like Candida (a yeast associated with vaginal infections), and other pathogens responsible for sexually transmitted diseases.

In the eyes, tears contain the chemical mediators lysozyme and lactoferrin, both of which are capable of eliminating microbes that have found their way to the surface of the eyes. Lysozyme cleaves the bond between NAG and NAM in peptidoglycan, a component of the cell wall in bacteria. It is more effective against gram-positive bacteria, which lack the protective outer membrane associated with gram-negative bacteria. Lactoferrin inhibits microbial growth by chemically binding and sequestering iron. This effectually starves many microbes that require iron for growth.

In the ears, cerumen (earwax) exhibits antimicrobial properties due to the presence of fatty acids, which lower the pH to between 3 and 5.

The respiratory tract uses various chemical mediators in the nasal passages, trachea, and lungs. The mucus produced in the nasal passages contains a mix of antimicrobial molecules similar to those found in tears and saliva (e.g., lysozyme, lactoferrin, lactoperoxidase). Secretions in the trachea and lungs also contain lysozyme and lactoferrin, as well as a diverse group of additional chemical mediators, such as the lipoprotein complex called surfactant, which has antibacterial properties.

**Exercise 4.2.1**

- Explain the difference between endogenous and exogenous mediators
- Describe how pH affects antimicrobial defenses

## Antimicrobial Peptides

The **antimicrobial peptides (AMPs)** are a special class of nonspecific cell-derived mediators with broad-spectrum antimicrobial properties. Some AMPs are produced routinely by the body, whereas others are primarily produced (or produced in greater quantities) in response to the presence of an invading pathogen. Research has begun exploring how AMPs can be used in the diagnosis and treatment of disease.

AMPs may induce cell damage in microorganisms in a variety of ways, including by inflicting damage to membranes, destroying DNA and RNA, or interfering with cell-wall synthesis. Depending on the specific antimicrobial mechanism, a particular AMP may inhibit only certain groups of microbes (e.g., gram-positive or gram-negative bacteria) or it may be more broadly effective against bacteria, fungi, protozoa, and viruses. Many AMPs are found on the skin, but they can also be found in other regions of the body.

A family of AMPs called defensins can be produced by epithelial cells throughout the body as well as by cellular defenses such as macrophages and neutrophils (see Cellular Defenses). Defensins may be secreted or act inside host cells; they combat microorganisms by damaging their plasma membranes. AMPs called bacteriocins are produced exogenously by certain members of the resident microbiota within the gastrointestinal tract. The genes coding for these types of AMPs are often carried on plasmids and can be passed between different species within the resident microbiota through lateral or horizontal gene transfer.

There are numerous other AMPs throughout the body. The characteristics of a few of the more significant AMPs are summarized

in ***Table*** 4.2.1.

*Table* 4.2.1: *Characteristics of Selected Antimicrobial Peptides (AMPs)*

| AMP | Secreted by | Body site | Pathogens inhibited | Mode of action |
|---|---|---|---|---|
| Bacteriocins | Resident microbiota | Gastrointestinal tract | Bacteria | Disrupt membrane |
| Cathelicidin | Epithelial cells, macrophages, and other cell types | Skin | Bacteria and fungi | Disrupts membrane |
| Defensins | Epithelial cells, macrophages, neutrophils | Throughout the body | Fungi, bacteria, and many viruses | Disrupt membrane |
| Dermicidin | Sweat glands | Skin | Bacteria and fungi | Disrupts membrane integrity and ion channels |
| Histatins | Salivary glands | Oral cavity | Fungi | Disrupt intracellular function |

**Exercise 4.2.2**

- Why are antimicrobial peptides (AMPs) considered nonspecific defenses?

## Plasma Protein Mediators

Many nonspecific innate immune factors are found in **plasma**, the fluid portion of blood. Plasma contains electrolytes, sugars, lipids, and proteins, each of which helps to maintain homeostasis (i.e., stable internal body functioning), and contains the proteins involved in the clotting of blood. Additional proteins found in blood plasma, such as acute-phase proteins, complement proteins, and cytokines, are involved in the nonspecific innate immune response.

**Micro Connections**

**Plasma versus Serum**

There are two terms for the fluid portion of blood: plasma and serum. How do they differ if they are both fluid and lack cells? The fluid portion of blood left over after coagulation (blood cell clotting) has taken place is serum. Although molecules such as many vitamins, electrolytes, certain sugars, complement proteins, and antibodies are still present in serum, clotting factors are largely depleted. Plasma, conversely, still contains all the clotting elements. To obtain plasma from blood, an anticoagulant must be used to prevent clotting. Examples of anticoagulants include heparin and ethylene diamine tetraacetic acid (EDTA). Because clotting is inhibited, once obtained, the sample must be gently spun down in a centrifuge. The heavier, denser blood cells form a pellet at the bottom of a centrifuge tube, while the fluid plasma portion, which is lighter and less dense, remains above the cell pellet.

### Acute-Phase Proteins

The **acute-phase proteins** are another class of antimicrobial mediators. Acute-phase proteins are primarily produced in the liver and secreted into the blood in response to inflammatory molecules from the immune system. Examples of acute-phase proteins include C-reactive protein, serum amyloid A, ferritin, transferrin, fibrinogen, and mannose- binding lectin. Each of these proteins has a different chemical structure and inhibits or destroys microbes in some way (***Table*** 4.2.2).

*Table* 4.2.2: *Some Acute-Phase Proteins and Their Functions*

| | |
|---|---|
| C-reactive protein | Coats bacteria (opsonization), preparing them for ingestion by phagocytes |
| Serum amyloid A | |
| Ferritin | Bind and sequester iron, thereby inhibiting the growth of pathogens |

| | |
|---|---|
| Transferrin | |
| Fibrinogen | Involved in formation of blood clots that trap bacterial pathogens |
| Mannose-binding lectin | Activates complement cascade |

## The Complement System

The **complement system** is a group of plasma protein mediators that can act as an innate nonspecific defense while also serving to connect innate and adaptive immunity (discussed in the next chapter). The complement system is composed of more than 30 proteins (including C1 through C9) that normally circulate as precursor proteins in blood. These precursor proteins become activated when stimulated or triggered by a variety of factors, including the presence of microorganisms. Complement proteins are considered part of innate nonspecific immunity because they are always present in the blood and tissue fluids, allowing them to be activated quickly. Also, when activated through the alternative pathway (described later in this section), complement proteins target pathogens in a nonspecific manner.

The process by which circulating complement precursors become functional is called **complement activation**. This process is a cascade that can be triggered by one of three different mechanisms, known as the alternative, classical, and lectin pathways.

The alternative pathway is initiated by the spontaneous activation of the complement protein C3. The hydrolysis of C3 produces two products, C3a and C3b. When no invader microbes are present, C3b is very quickly degraded in a hydrolysis reaction using the water in the blood. However, if invading microbes are present, C3b attaches to the surface of these microbes. Once attached, C3b will recruit other complement proteins in a cascade (***Figure*** 4.2.2).

The classical pathway provides a more efficient mechanism of activating the complement cascade, but it depends upon the production of antibodies by the specific adaptive immune defenses. To initiate the classical pathway, a specific antibody must first bind to the pathogen to form an antibody-antigen complex. This activates the first protein in the complement cascade, the C1 complex. The C1 complex is a multipart protein complex, and each component participates in the full activation of the overall complex. Following recruitment and activation of the C1 complex, the remaining classical pathway complement proteins are recruited and activated in a cascading sequence (***Figure*** 4.2.2).

The lectin activation pathway is similar to the classical pathway, but it is triggered by the binding of mannose-binding lectin, an acute-phase protein, to carbohydrates on the microbial surface. Like other acute-phase proteins, lectins are produced by liver cells and are commonly upregulated in response to inflammatory signals received by the body during an infection (***Figure*** 4.2.2).

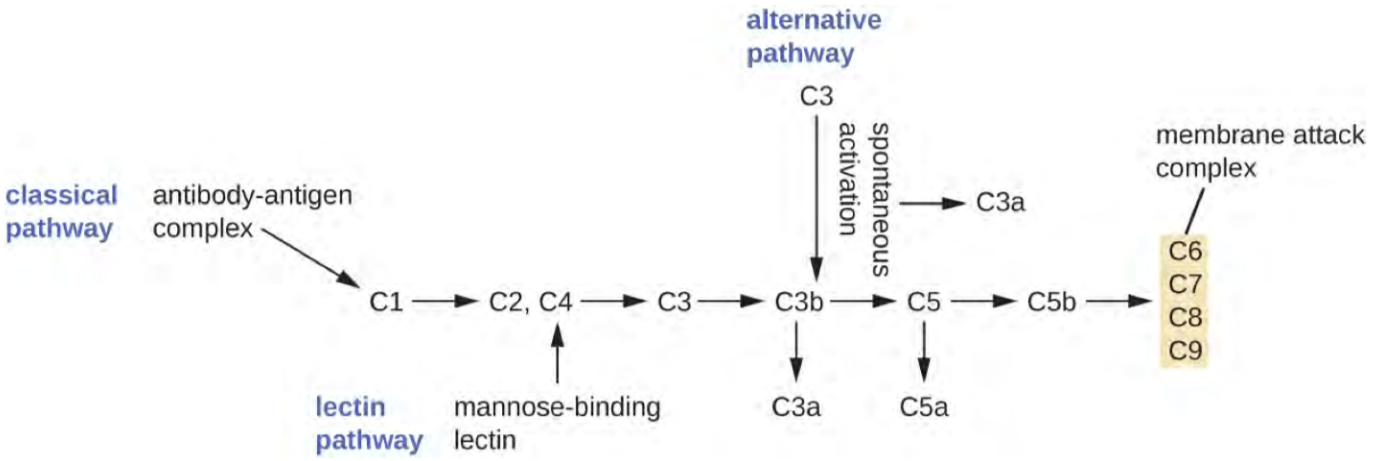



Figure 4.2.2: The three complement activation pathways have different triggers, as shown here, but all three result in the activation of the complement protein C3, which produces C3a and C3b. The latter binds to the surface of the target cell and then works with other complement proteins to cleave C5 into C5a and C5b. C5b also binds to the cell surface and then recruits C6 through C9; these molecules form a ring structure called the membrane attack complex (MAC), which punches through the cell membrane of the invading pathogen, causing it to swell and burst.

Although each complement activation pathway is initiated in a different way, they all provide the same protective outcomes: opsonization, inflammation, chemotaxis, and cytolysis. The term **opsonization** refers to the coating of a pathogen by a

chemical substance (called an **opsonin**) that allows phagocytic cells to recognize, engulf, and destroy it more easily. Opsonins from the complement cascade include C1q, C3b, and C4b. Additional important opsonins include mannose-binding proteins and antibodies. The complement fragments C3a and C5a are well-characterized anaphylatoxins with potent proinflammatory functions. Anaphylatoxins activate mast cells, causing degranulation and the release of inflammatory chemical signals, including mediators that cause vasodilation and increased vascular permeability. C5a is also one of the most potent chemoattractants for neutrophils and other white blood cells, cellular defenses that will be discussed in the next section.

The complement proteins C6, C7, C8, and C9 assemble into a **membrane attack complex (MAC)**, which allows C9 to polymerize into pores in the membranes of gram-negative bacteria. These pores allow water, ions, and other molecules to move freely in and out of the targeted cells, eventually leading to cell lysis and death of the pathogen (***Figure*** 4.2.2). However, the MAC is only effective against gram-negative bacteria; it cannot penetrate the thick layer of peptidoglycan associated with cell walls of gram-positive bacteria. Since the MAC does not pose a lethal threat to gram-positive bacterial pathogens, complement-mediated opsonization is more important for their clearance.

## Cytokines

**Cytokines** are soluble proteins that act as communication signals between cells. In a nonspecific innate immune response, various cytokines may be released to stimulate production of chemical mediators or other cell functions, such as cell proliferation, cell differentiation, inhibition of cell division, apoptosis, and chemotaxis.

When a cytokine binds to its target receptor, the effect can vary widely depending on the type of cytokine and the type of cell or receptor to which it has bound. The function of a particular cytokine can be described as autocrine, paracrine, or endocrine (***Figure*** 4.2.3). In **autocrine function**, the same cell that releases the cytokine is the recipient of the signal; in other words, autocrine function is a form of self-stimulation by a cell. In contrast, **paracrine function** involves the release of cytokines from one cell to other nearby cells, stimulating some response from the recipient cells. Last, **endocrine function** occurs when cells release cytokines into the bloodstream to be carried to target cells much farther away.

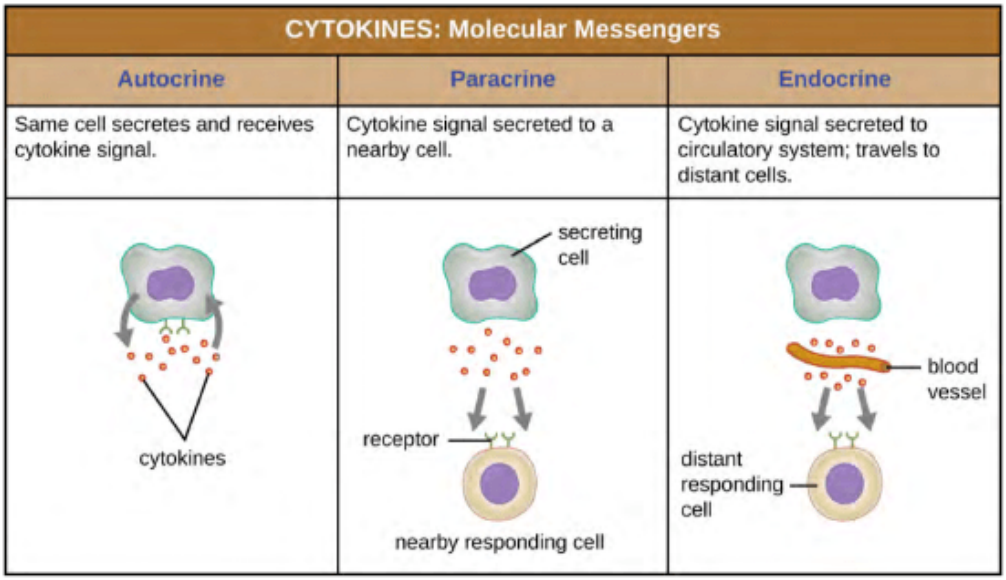



Figure 4.2.3: Autocrine, paracrine, and endocrine actions describe which cells are targeted by cytokines and how far the cytokines must travel to bind to their intended target cells' receptors.

Three important classes of cytokines are the interleukins, chemokines, and interferons. The **interleukins** were originally thought to be produced only by leukocytes (white blood cells) and to only stimulate leukocytes, thus the reasons for their name. Although interleukins are involved in modulating almost every function of the immune system, their role in the body is not restricted to immunity. Interleukins are also produced by and stimulate a variety of cells unrelated to immune defenses.

The **chemokines** are chemotactic factors that recruit leukocytes to sites of infection, tissue damage, and inflammation. In contrast to more general chemotactic factors, like complement factor C5a, chemokines are very specific in the subsets of leukocytes they recruit.

Interferons are a diverse group of immune signaling molecules and are especially important in our defense against viruses. Type I **interferons** (interferon-α and interferon-β) are produced and released by cells infected with virus. These interferons stimulate nearby cells to stop production of mRNA, destroy RNA already produced, and reduce protein synthesis. These cellular changes inhibit viral replication and production of mature virus, slowing the spread of the virus. Type I interferons also stimulate various immune cells involved in viral clearance to more aggressively attack virus-infected cells. Type II interferon (interferon-γ) is an important activator of immune cells (***Figure*** 4.2.4).

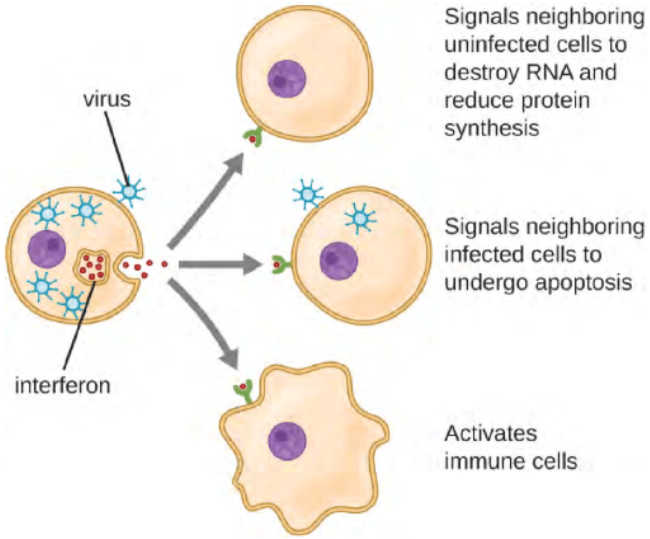



Figure 4.2.4: Interferons are cytokines released by a cell infected with a virus. Interferon-α and interferon-β signal uninfected neighboring cells to inhibit mRNA synthesis, destroy RNA, and reduce protein synthesis (top arrow). Interferon-α and interferon-β also promote apoptosis in cells infected with the virus (middle arrow). Interferon-γ alerts neighboring immune cells to an attack (bottom arrow). Although interferons do not cure the cell releasing them or other infected cells, which will soon die, their release may prevent additional cells from becoming infected, thus stemming the infection.

## Inflammation-Eliciting Mediators

Many of the chemical mediators discussed in this section contribute in some way to inflammation and fever, which are nonspecific immune responses discussed in more detail in Inflammation and Fever. Cytokines stimulate the production of acute-phase proteins such as C-reactive protein and mannose-binding lectin in the liver. These acute- phase proteins act as opsonins, activating complement cascades through the lectin pathway.

Some cytokines also bind mast cells and basophils, inducing them to release **histamine**, a proinflammatory compound. Histamine receptors are found on a variety of cells and mediate proinflammatory events, such as bronchoconstriction (tightening of the airways) and smooth muscle contraction.

In addition to histamine, mast cells may release other chemical mediators, such as **leukotrienes**. Leukotrienes are lipid-based proinflammatory mediators that are produced from the metabolism of arachidonic acid in the cell membrane of leukocytes and tissue cells. Compared with the proinflammatory effects of histamine, those of leukotrienes are more potent and longer lasting. Together, these chemical mediators can induce coughing, vomiting, and diarrhea, which serve to expel pathogens from the body.

Certain cytokines also stimulate the production of prostaglandins, chemical mediators that promote the inflammatory effects of kinins and histamines. Prostaglandins can also help to set the body temperature higher, leading to fever, which promotes the activities of white blood cells and slightly inhibits the growth of pathogenic microbes (see Inflammation and Fever).

Another inflammatory mediator, **bradykinin**, contributes to edema, which occurs when fluids and leukocytes leak out of the bloodstream and into tissues. It binds to receptors on cells in the capillary walls, causing the capillaries to dilate and become more permeable to fluids.

## Exercise 4.2.3

- What do the three complement activation pathways have in common?
- Explain autocrine, paracrine, and endocrine signals.
- Name two important inflammation-eliciting mediators.

## Clinical Focus

**Part 2**

To relieve the constriction of her airways, Angela is immediately treated with antihistamines and administered corticosteroids through an inhaler, and then monitored for a period of time. Though her condition does not worsen, the drugs do not seem to be alleviating her condition. She is admitted to the hospital for further observation, testing, and treatment.

Following admission, a clinician conducts allergy testing to try to determine if something in her environment might be triggering an allergic inflammatory response. A doctor orders blood analysis to check for levels of particular cytokines. A sputum sample is also taken and sent to the lab for microbial staining, culturing, and identification of pathogens that could be causing an infection.

- Which aspects of the innate immune system could be contributing to Angela's airway constriction?
- Why was Angela treated with antihistamines?
- Why would the doctor be interested in levels of cytokines in Angela's blood?

*Jump to the next Clinical Focus box. Go back to the previous Clinical Focus box.*

***Table*** 4.2.3 provides a summary of the chemical defenses discussed in this section.

*Table 4.2.3: Chemical Defenses of Nonspecific Innate Immunity*

| Defense | Examples | Function |
|---|---|---|
| Chemicals and enzymes in body fluids | Sebum from sebaceous glands | Provides oil barrier protecting hair follicle pores from pathogens |
| | Oleic acid from sebum and skin microbiota | Lowers pH to inhibit pathogens |
| | Lysozyme in secretions | Kills bacteria by attacking cell wall |
| | Acid in stomach, urine, and vagina | Inhibits or kills bacteria |
| | Digestive enzymes and bile | Kill bacteria |
| | Lactoferrin and transferrin | Bind and sequester iron, inhibiting bacterial growth |
| | Surfactant in lungs | Kills bacteria |
| Antimicrobial peptides | Defensins, bacteriocins, dermicidin, cathelicidin, histatins, | Kill bacteria by attacking membranes or interfering with cell functions |
| Plasma protein mediators | Acute-phase proteins (C-reactive protein, serum amyloid A, ferritin, fibrinogen, transferrin, and mannose-binding lectin) | Inhibit the growth of bacteria and assist in the trapping and killing of bacteria |
| | Complements C3b and C4b | Opsonization of pathogens to aid phagocytosis |
| | Complement C5a | Chemoattractant for phagocytes |
| | Complements C3a and C5a | Proinflammatory anaphylatoxins |
| Cytokines | Interleukins | Stimulate and modulate most functions of immune system |
| | Chemokines | Recruit white blood cells to infected area |

| Defense | Examples | Function |
|---|---|---|
| | Interferons | Alert cells to viral infection, induce apoptosis of virus-infected cells, induce antiviral defenses in infected and nearby uninfected cells, stimulate immune cells to attack virus-infected cells |
| Inflammation-eliciting mediators | Histamine | Promotes vasodilation, bronchoconstriction, smooth muscle contraction, increased secretion and mucus production |
| | Leukotrienes | Promote inflammation; stronger and longer lasting than histamine |
| | Prostaglandins | Promote inflammation and fever |
| | Bradykinin | Increases vasodilation and vascular permeability, leading to edema |

## Key Concepts and Summary

- Numerous **chemical mediators** produced endogenously and exogenously exhibit nonspecific antimicrobial functions.
- Many chemical mediators are found in body fluids such as sebum, saliva, mucus, gastric and intestinal fluids, urine, tears, cerumen, and vaginal secretions.
- **Antimicrobial peptides (AMPs)** found on the skin and in other areas of the body are largely produced in response to the presence of pathogens. These include dermcidin, cathelicidin, defensins, histatins, and bacteriocins.
- **Plasma** contains various proteins that serve as chemical mediators, including **acute-phase proteins**, **complement proteins**, and **cytokines**.
- The **complement system** involves numerous precursor proteins that circulate in plasma. These proteins become activated in a cascading sequence in the presence of microbes, resulting in the **opsonization** of pathogens, chemoattraction of leukocytes, induction of inflammation, and cytolysis through the formation of a **membrane attack complex (MAC)**.
- **Cytokines** are proteins that facilitate various nonspecific responses by innate immune cells, including production of other chemical mediators, cell proliferation, cell death, and differentiation.
- Cytokines play a key role in the inflammatory response, triggering production of inflammation-eliciting mediators such as acute-phase proteins, **histamine**, leukotrienes, **prostaglandins**, and **bradykinin**.

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# 4.3: Cellular Defenses

**Learning Objectives**

- Identify and describe the components of blood
- Explain the process by which the formed elements of blood are formed (hematopoiesis)
- Describe the characteristics of formed elements found in peripheral blood, as well as their respective functions within the innate immune system

In the previous section, we discussed some of the chemical mediators found in plasma, the fluid portion of blood. The nonfluid portion of blood consists of various types of formed elements, so called because they are all formed from the same stem cells found in bone marrow. The three major categories of formed elements are: red blood cells (RBCs), also called **erythrocytes**; **platelets**, also called **thrombocytes**; and white blood cells (WBCs), also called **leukocytes**.

Red blood cells are primarily responsible for carrying oxygen to tissues. Platelets are cellular fragments that participate in blood clot formation and tissue repair. Several different types of WBCs participate in various nonspecific mechanisms of innate and adaptive immunity. In this section, we will focus primarily on the innate mechanisms of various types of WBCs.

## Hematopoiesis

All of the formed elements of blood are derived from pluripotent hematopoietic stem cells (HSCs) in the bone marrow. As the HSCs make copies of themselves in the bone marrow, individual cells receive different cues from the body that control how they develop and mature. As a result, the HSCs differentiate into different types of blood cells that, once mature, circulate in peripheral blood. This process of differentiation, called **hematopoiesis**, is shown in more detail in ***Figure*** 4.3.1.

In terms of sheer numbers, the vast majority of HSCs become erythrocytes. Much smaller numbers become leukocytes and platelets. Leukocytes can be further subdivided into **granulocytes**, which are characterized by numerous granules visible in the cytoplasm, and agranulocytes, which lack granules. ***Figure*** 4.3.2 provides an overview of the various types of formed elements, including their relative numbers, primary function, and lifespans.

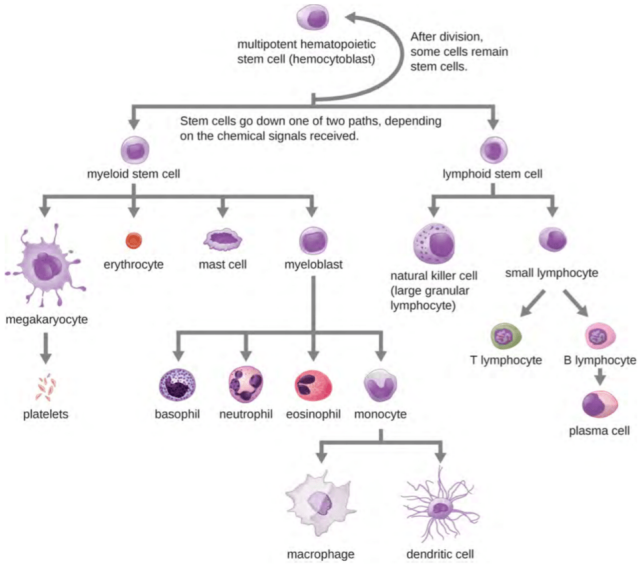



Figure 4.3.1: All the formed elements of the blood arise by differentiation of hematopoietic stem cells in the bone marrow.

| Formed Element | Major Subtypes | | Numbers Present per Microliter (μL) and Mean (Range) | Appearance in a Standard Blood Smear | Summary of Functions | Comments |
|---|---|---|---|---|---|---|
| *Erythrocytes (red blood cells)* | | | 5.2 million (4.4–6.0 million) | Flattened biconcave disk; no nucleus; pale red | Transport oxygen and some carbon dioxide between tissue and lungs | Lifespan of approximately 120 days |
| *Leukocytes (white blood cells)* | | | 7000 (5000–10,000) | Obvious dark-staining nucleus | All function in body defenses | Exit capillaries and move into tissues; lifespan of usually a few hours or days |
| | *Granulocytes, including neutrophils, eosinophils, and basophils* | *Total leukocytes (%)* | 4360 (1800–9950) | Abundant granules in cytoplasm; nucleus normally lobed | Nonspecific (innate) resistance to disease | Classified according to membrane-bound granules in cytoplasm |
| | Neutrophils | 50–70 | 4150 (1800–7300) | Nucleus lobes increase with age; pale lilac granules | Phagocytic; particularly effective against bacteria; release cytotoxic chemicals from granules | Most common leukocyte; lifespan of minutes to days |
| | Eosinophils | 1–3 | 165 (0–700) | Nucleus generally two-lobed; bright red-orange granules | Phagocytic cells; particularly effective with antigen-antibody complexes; release antihistamines; combat parasitic infections | Lifespan of minutes to days |
| | Basophils | <1 | 44 (0–150) | Nucleus generally two-lobed but difficult to see due to presence of heavy, dense, dark purple granules | Pro-inflammatory | Least common leukocyte; lifespan unknown |
| | *Agranulocytes, including lymphocytes and monocytes* | | 2640 (1700–4950) | Lack abundant granules in cytoplasm; have a simple-shaped nucleus that may be indented | Body defenses | Group consists of two major cell types from different lineages |
| | Lymphocytes | 20–40 | 2185 (1500–4000) | Spherical cells with a single, often large, nucleus occupying much of the cell's volume; stains purple; seen in large (natural killer cells) and small (B and T cells) variants | Primarily specific (adaptive) immunity: T cells directly attack other cells (cellular immunity); B cells release antibodies (humoral immunity); natural killer cells are similar to T cells but nonspecific | Initial cells originate in bone marrow, but secondary production occurs in lymphatic tissue; several distinct subtypes; memory cells form after exposure to a pathogen and rapidly increase responses to subsequent exposure; lifespan of many years |
| | Monocytes | 1–6 | 455 (200–950) | Largest leukocyte; has an indented or horseshoe-shaped nucleus | Very effective phagocytic cells engulfing pathogens or worn-out cells; also serve as antigen-presenting cells (APCs) or other components of the immune system | Produced in red bone marrow; referred to as macrophages and dendritic cells after leaving the circulation |
| *Platelets* | | | 350,000 (150,000–500,000) | Cellular fragments surrounded by a plasma membrane and containing granules; stains purple | Hemostasis; release growth factors for repair and healing of tissue | Formed from megakaryocytes that remain in the red bone marrow and shed platelets into circulation |

Figure 4.3.2: Formed elements of blood include erythrocytes (red blood cells), leukocytes (white blood cells), and platelets.

## Granulocytes

The various types of granulocytes can be distinguished from one another in a blood smear by the appearance of their nuclei and the contents of their granules, which confer different traits, functions, and staining properties. The **neutrophils**, also called **polymorphonuclear neutrophils (PMNs)**, have a nucleus with three to five lobes and small, numerous, lilac-colored granules. Each lobe of the nucleus is connected by a thin strand of material to the other lobes. The **eosinophils** have fewer lobes in the nucleus (typically 2–3) and larger granules that stain reddish-orange. The **basophils** have a two-lobed nucleus and large granules that stain dark blue or purple (***Figure*** 4.3.3).

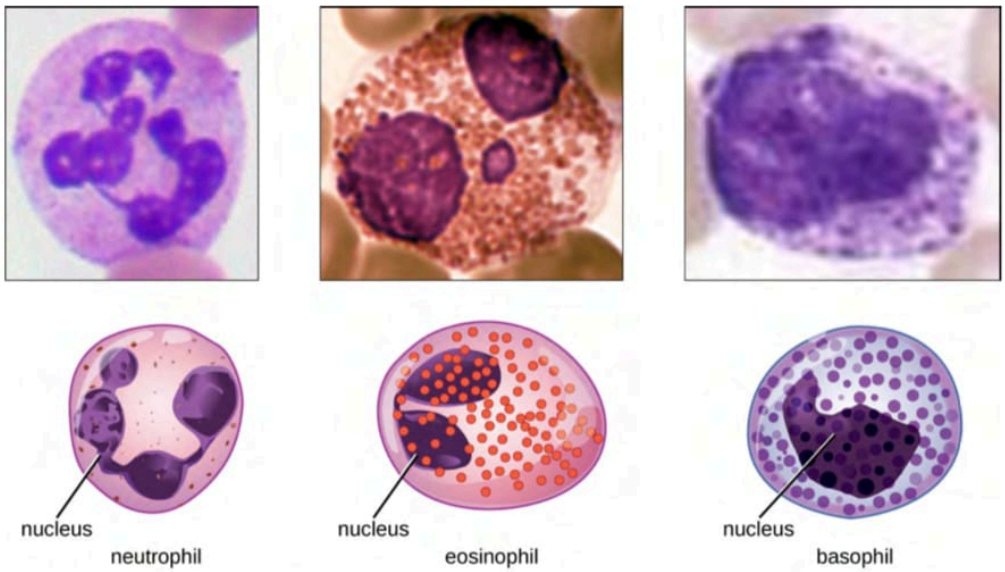



Figure 4.3.3: Granulocytes can be distinguished by the number of lobes in their nuclei and the staining properties of their granules. (credit "neutrophil" micrograph: modification of work by Ed Uthman)

## Neutrophils (PMNs)

Neutrophils (PMNs) are frequently involved in the elimination and destruction of extracellular bacteria. They are capable of migrating through the walls of blood vessels to areas of bacterial infection and tissue damage, where they seek out and kill infectious bacteria. PMN granules contain a variety of defensins and hydrolytic enzymes that help them destroy bacteria through

phagocytosis (described in more detail in Pathogen Recognition and Phagocytosis) In addition, when many neutrophils are brought into an infected area, they can be stimulated to release toxic molecules into the surrounding tissue to better clear infectious agents. This is called degranulation.

Another mechanism used by neutrophils is neutrophil extracellular traps (NETs), which are extruded meshes of chromatin that are closely associated with antimicrobial granule proteins and components. Chromatin is DNA with associated proteins (usually histone proteins, around which DNA wraps for organization and packing within a cell). By creating and releasing a mesh or lattice-like structure of chromatin that is coupled with antimicrobial proteins, the neutrophils can mount a highly concentrated and efficient attack against nearby pathogens. Proteins frequently associated with NETs include lactoferrin, gelatinase, cathepsin G, and myeloperoxidase. Each has a different means of promoting antimicrobial activity, helping neutrophils eliminate pathogens. The toxic proteins in NETs may kill some of the body's own cells along with invading pathogens. However, this collateral damage can be repaired after the danger of the infection has been eliminated.

As neutrophils fight an infection, a visible accumulation of leukocytes, cellular debris, and bacteria at the site of infection can be observed. This buildup is what we call **pus** (also known as purulent or suppurative discharge or drainage). The presence of pus is a sign that the immune defenses have been activated against an infection; historically, some physicians believed that inducing pus formation could actually promote the healing of wounds. The practice of promoting "laudable pus" (by, for instance, wrapping a wound in greasy wool soaked in wine) dates back to the ancient physician Galen in the 2nd century AD, and was practiced in variant forms until the 17th century (though it was not universally accepted). Today, this method is no longer practiced because we now know that it is not effective. Although a small amount of pus formation can indicate a strong immune response, artificially inducing pus formation does not promote recovery.

## Eosinophils

Eosinophils are granulocytes that protect against protozoa and helminths; they also play a role in allergic reactions. The granules of eosinophils, which readily absorb the acidic reddish dye eosin, contain histamine, degradative enzymes, and a compound known as major basic protein (MBP) (***Figure*** 4.3.3). MBP binds to the surface carbohydrates of parasites, and this binding is associated with disruption of the cell membrane and membrane permeability.

## Basophils

Basophils have cytoplasmic granules of varied size and are named for their granules' ability to absorb the basic dye methylene blue (***Figure*** 4.3.3). Their stimulation and degranulation can result from multiple triggering events. Activated complement fragments C3a and C5a, produced in the activation cascades of complement proteins, act as anaphylatoxins by inducing degranulation of basophils and inflammatory responses. This cell type is important in allergic reactions and other responses that involve inflammation. One of the most abundant components of basophil granules is histamine, which is released along with other chemical factors when the basophil is stimulated. These chemicals can be chemotactic and can help to open the gaps between cells in the blood vessels. Other mechanisms for basophil triggering require the assistance of antibodies, as discussed in B Lymphocytes and Humoral Immunity.

## Mast Cells

Hematopoiesis also gives rise to **mast cells**, which appear to be derived from the same common myeloid progenitor cell as neutrophils, eosinophils, and basophils. Functionally, mast cells are very similar to basophils, containing many of the same components in their granules (e.g., histamine) and playing a similar role in allergic responses and other inflammatory reactions. However, unlike basophils, mast cells leave the circulating blood and are most frequently found residing in tissues. They are often associated with blood vessels and nerves or found close to surfaces that interface with the external environment, such as the skin and mucous membranes in various regions of the body (***Figure*** 4.3.4).

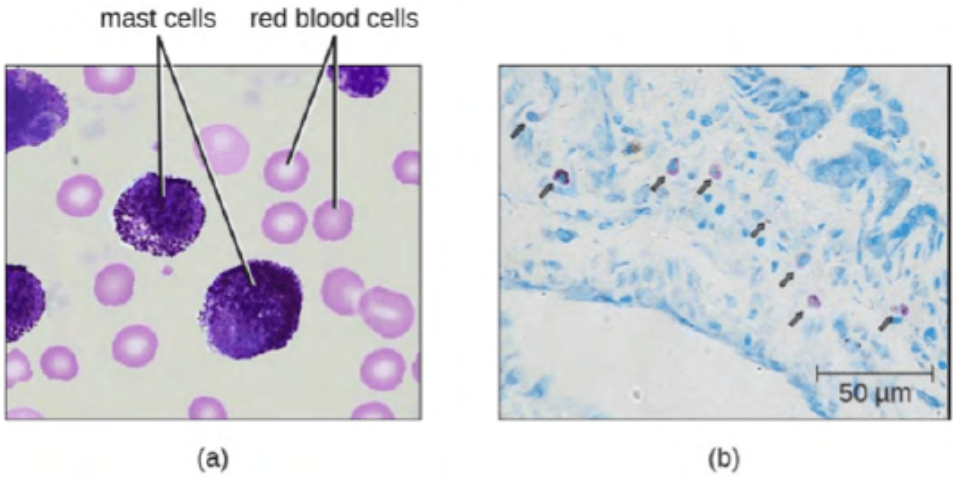



Figure 4.3.4: Mast cells function similarly to basophils by inducing and promoting inflammatory responses. (a) This figure shows mast cells in blood. In a blood smear, they are difficult to differentiate from basophils (b). Unlike basophils, mast cells migrate from the blood into various tissues. (credit right: modification of work by Greenland JR, Xu X, Sayah DM, Liu FC, Jones KD, Looney MR, Caughey GH)

**Exercise 4.3.1**

- Describe the granules and nuclei of neutrophils, eosinophils, basophils, and mast cells.
- Name three antimicrobial mechanisms of neutrophils

**Clinical Focus**

**Part 3**

Angela's tests come back negative for all common allergens, and her sputum samples contain no abnormal presence of pathogenic microbes or elevated levels of members of the normal respiratory microbiota. She does, however, have elevated levels of inflammatory cytokines in her blood.

The swelling of her airway has still not responded to treatment with antihistamines or corticosteroids. Additional blood work shows that Angela has a mildly elevated white blood cell count but normal antibody levels. Also, she has a lower-than-normal level of the complement protein C4.

- What does this new information reveal about the cause of Angela's constricted airways?
- What are some possible conditions that could lead to low levels of complement proteins?

*Jump to the next Clinical Focus box. Go back to the previous Clinical Focus box*

## Agranulocytes

As their name suggests, **agranulocytes** lack visible granules in the cytoplasm. Agranulocytes can be categorized as lymphocytes or monocytes (***Figure*** 4.3.2). Among the lymphocytes are natural killer cells, which play an important role in nonspecific innate immune defenses. Lymphocytes also include the B cells and T cells, which are discussed in the next chapter because they are central players in the specific adaptive immune defenses. The monocytes differentiate into macrophages and dendritic cells, which are collectively referred to as the mononuclear phagocyte system.

### Natural Killer Cells

Most lymphocytes are primarily involved in the specific adaptive immune response, and thus will be discussed in the following chapter. An exception is the **natural killer cells (NK cells)**; these mononuclear lymphocytes use nonspecific mechanisms to

recognize and destroy cells that are abnormal in some way. Cancer cells and cells infected with viruses are two examples of cellular abnormalities that are targeted by NK cells. Recognition of such cells involves a complex process of identifying inhibitory and activating molecular markers on the surface of the target cell. Molecular markers that make up the major histocompatibility complex (MHC) are expressed by healthy cells as an indication of "self." This will be covered in more detail in next chapter. NK cells are able to recognize normal MHC markers on the surface of healthy cells, and these MHC markers serve as an inhibitory signal preventing NK cell activation. However, cancer cells and virus-infected cells actively diminish or eliminate expression of MHC markers on their surface. When these MHC markers are diminished or absent, the NK cell interprets this as an abnormality and a cell in distress. This is one part of the NK cell activation process (***Figure*** 4.3.5). NK cells are also activated by binding to activating molecular molecules on the target cell. These activating molecular molecules include "altered self" or "nonself" molecules. When a NK cell recognizes a decrease in inhibitory normal MHC molecules and an increase in activating molecules on the surface of a cell, the NK cell will be activated to eliminate the cell in distress.

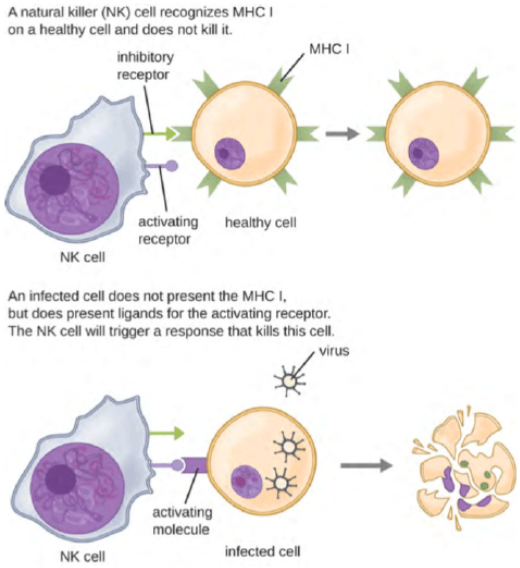



Figure 4.3.5: Natural killer (NK) cells are inhibited by the presence of the major histocompatibility cell (MHC) receptor on healthy cells. Cancer cells and virus-infected cells have reduced expression of MHC and increased expression of activating molecules. When a NK cell recognizes decreased MHC and increased activating molecules, it will kill the abnormal cell.

Once a cell has been recognized as a target, the NK cell can use several different mechanisms to kill its target. For example, it may express cytotoxic membrane proteins and cytokines that stimulate the target cell to undergo apoptosis, or controlled cell suicide. NK cells may also use perforin-mediated cytotoxicity to induce apoptosis in target cells. This mechanism relies on two toxins released from granules in the cytoplasm of the NK cell: **perforin**, a protein that creates pores in the target cell, and **granzymes**, proteases that enter through the pores into the target cell's cytoplasm, where they trigger a cascade of protein activation that leads to apoptosis. The NK cell binds to the abnormal target cell, releases its destructive payload, and detaches from the target cell. While the target cell undergoes apoptosis, the NK cell synthesizes more perforin and proteases to use on its next target.

NK cells contain these toxic compounds in granules in their cytoplasm. When stained, the granules are azurophilic and can be visualized under a light microscope (***Figure*** 4.3.6). Even though they have granules, NK cells are not considered granulocytes because their granules are far less numerous than those found in true granulocytes. Furthermore, NK cells have a different lineage than granulocytes, arising from lymphoid rather than myeloid stem cells (***Figure*** 4.3.1).

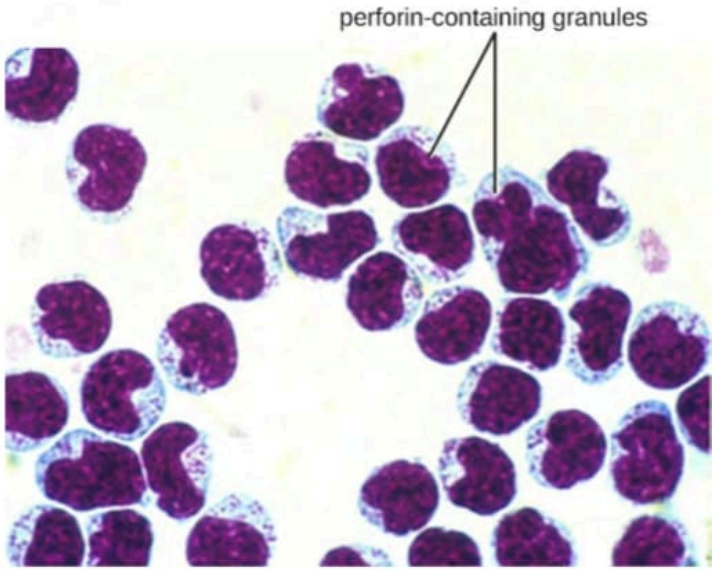



Figure 4.3.6: Natural killer cell with perforin-containing granules. (credit: modification of work by Rolstad B)

## Monocytes

The largest of the white blood cells, **monocytes** have a nucleus that lacks lobes, and they also lack granules in the cytoplasm (***Figure*** 4.3.7). Nevertheless, they are effective phagocytes, engulfing pathogens and apoptotic cells to help fight infection.

When monocytes leave the bloodstream and enter a specific body tissue, they differentiate into tissue-specific phagocytes called **macrophages** and **dendritic** cells. They are particularly important residents of lymphoid tissue, as well as nonlymphoid sites and organs. Macrophages and dendritic cells can reside in body tissues for significant lengths of time. Macrophages in specific body tissues develop characteristics suited to the particular tissue. Not only do they provide immune protection for the tissue in which they reside but they also support normal function of their neighboring tissue cells through the production of cytokines. Macrophages are given tissue-specific names, and a few examples of tissue-specific macrophages are listed in ***Table*** 4.3.1. Dendritic cells are important sentinels residing in the skin and mucous membranes, which are portals of entry for many pathogens. Monocytes, macrophages, and dendritic cells are all highly phagocytic and important promoters of the immune response through their production and release of cytokines. These cells provide an essential bridge between innate and adaptive immune responses, as discussed in the next section as well as the next chapter.

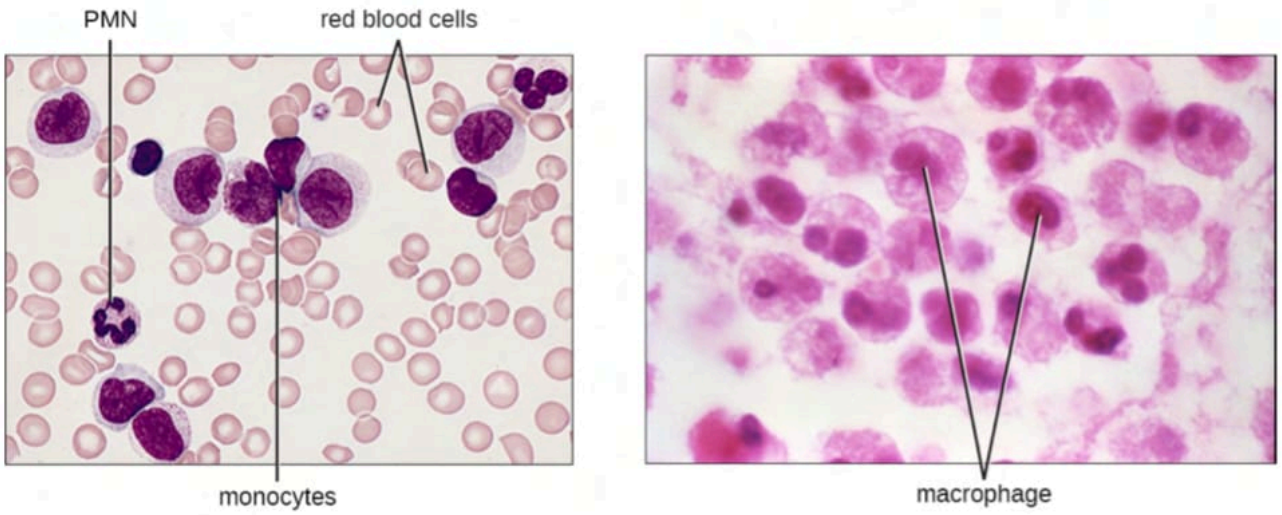



Figure 4.3.7: Monocytes are large, agranular white blood cells with a nucleus that lacks lobes. When monocytes leave the bloodstream, they differentiate and become macrophages with tissue-specific properties. (credit left: modification of work by Armed Forces Institute of Pathology; credit right: modification of work by Centers for Disease Control and Prevention)

*Table 4.3.1: Macrophages Found in Various Body Tissues*

| Tissue | Macrophage |
|---|---|
| Brain and central nervous system | Microglial cells |
| Liver | Kupffer cells |
| Lungs | Alveolar macrophages (dust cells) |
| Peritoneal cavity | Peritoneal macrophages |

**Exercise 4.3.2**

- Describe the signals that activate natural killer cells.
- What is the difference between monocytes and macrophages?

## Key Concepts and Summary

- The **formed elements** of the blood include red blood cells (**erythrocytes**), white blood cells (**leukocytes**), and **platelets (thrombocytes)**. Of these, leukocytes are primarily involved in the immune response.
- All formed elements originate in the bone marrow as stem cells (HSCs) that differentiate through **hematopoiesis**.
- **Granulocytes** are leukocytes characterized by a lobed nucleus and granules in the cytoplasm. These include **neutrophils (PMNs)**, **eosinophils**, and **basophils**.
- Neutrophils are the leukocytes found in the largest numbers in the bloodstream and they primarily fight bacterial infections.
- Eosinophils target parasitic infections. Eosinophils and basophils are involved in allergic reactions. Both release histamine and other proinflammatory compounds from their granules upon stimulation.
- **Mast cells** function similarly to basophils but can be found in tissues outside the bloodstream.
- **Natural killer (NK)** cells are lymphocytes that recognize and kill abnormal or infected cells by releasing proteins that trigger apoptosis.
- **Monocytes** are large, mononuclear leukocytes that circulate in the bloodstream. They may leave the bloodstream and take up residence in body tissues, where they differentiate and become tissue-specific **macrophages** and **dendritic cells**.

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# 4.4: Pathogen Recognition and Phagocytosis

**Learning Objectives**

- Explain how leukocytes migrate from peripheral blood into infected tissues
- Explain the mechanisms by which leukocytes recognize pathogens
- Explain the process of phagocytosis and the mechanisms by which phagocytes destroy and degrade pathogens

Several of the cell types discussed in the previous section can be described as phagocytes—cells whose main function is to seek, ingest, and kill pathogens. This process, called phagocytosis, was first observed in starfish in the 1880s by Nobel Prize-winning zoologist Ilya Metchnikoff (1845–1916), who made the connection to white blood cells (WBCs) in humans and other animals. At the time, Pasteur and other scientists believed that WBCs were spreading pathogens rather than killing them (which is true for some diseases, such as tuberculosis). But in most cases, phagocytes provide a strong, swift, and effective defense against a broad range of microbes, making them a critical component of innate nonspecific immunity. This section will focus on the mechanisms by which phagocytes are able to seek, recognize, and destroy pathogens.

## Extravasation (Diapedesis) of Leukocytes

Some phagocytes are leukocytes (WBCs) that normally circulate in the bloodstream. To reach pathogens located in infected tissue, leukocytes must pass through the walls of small capillary blood vessels within tissues. This process, called **extravasation**, or **diapedesis**, is initiated by complement factor C5a, as well as cytokines released into the immediate vicinity by resident macrophages and tissue cells responding to the presence of the infectious agent (***Figure*** 4.4.1). Similar to C5a, many of these cytokines are proinflammatory and chemotactic, and they bind to cells of small capillary blood vessels, initiating a response in the endothelial cells lining the inside of the blood vessel walls. This response involves the upregulation and expression of various cellular adhesion molecules and receptors. Leukocytes passing through will stick slightly to the adhesion molecules, slowing down and rolling along the blood vessel walls near the infected area. When they reach a cellular junction, they will bind to even more of these adhesion molecules, flattening out and squeezing through the cellular junction in a process known as **transendothelial migration**. This mechanism of “rolling adhesion” allows leukocytes to exit the bloodstream and enter the infected areas, where they can begin phagocytosing the invading pathogens.

Note that extravasation does not occur in arteries or veins. These blood vessels are surrounded by thicker, multilayer protective walls, in contrast to the thin single-cell-layer walls of capillaries. Furthermore, the blood flow in arteries is too turbulent to allow for rolling adhesion. Also, some leukocytes tend to respond to an infection more quickly than others. The first to arrive typically are neutrophils, often within hours of a bacterial infection. By contract, monocytes may take several days to leave the bloodstream and differentiate into macrophages.

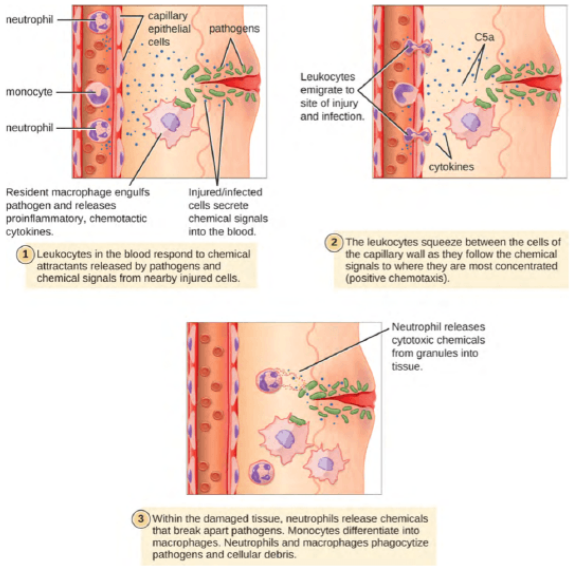



Figure 4.4.1: Damaged cells and macrophages that have ingested pathogens release cytokines that are proinflammatory and chemotactic for leukocytes. In addition, activation of complement at the site of infection results in production of the chemotactic and proinflammatory C5a. Leukocytes exit the blood vessel and follow the chemoattractant signal of cytokines and C5a to the site of infection. Granulocytes such as neutrophils release chemicals that destroy pathogens. They are also capable of phagocytosis and intracellular killing of bacterial pathogens.

**Link to Learning**

Watch the following videos on leukocyte extravasation and leukocyte rolling to learn more.

**Exercise 4.4.1**

- Explain the role of adhesion molecules in the process of extravasation.

## Pathogen Recognition

As described in the previous section, opsonization of pathogens by antibody; complement factors C1q, C3b, and C4b; and lectins can assist phagocytic cells in recognition of pathogens and attachment to initiate phagocytosis. However, not all pathogen recognition is opsonin dependent. Phagocytes can also recognize molecular structures that are common to many groups of pathogenic microbes. Such structures are called **pathogen-associated molecular patterns (PAMPs)**. Common PAMPs include the following:

- peptidoglycan, found in bacterial cell walls;
- flagellin, a protein found in bacterial flagella;
- lipopolysaccharide (LPS) from the outer membrane of gram-negative bacteria;
- lipopeptides, molecules expressed by most bacteria; and
- nucleic acids such as viral DNA or RNA.

Like numerous other PAMPs, these substances are integral to the structure of broad classes of microbes.

The structures that allow phagocytic cells to detect PAMPs are called **pattern recognition receptors (PRRs)**. One group of PRRs is the **toll-like receptors (TLRs)**, which bind to various PAMPs and communicate with the nucleus of the phagocyte to elicit a response. Many TLRs (and other PRRs) are located on the surface of a phagocyte, but some can also be found embedded in the membranes of interior compartments and organelles (***Figure*** 4.4.2). These interior PRRs can be useful for the binding and recognition of intracellular pathogens that may have gained access to the inside of the cell before phagocytosis could take place. Viral nucleic acids, for example, might encounter an interior PRR, triggering production of the antiviral cytokine interferon.

In addition to providing the first step of pathogen recognition, the interaction between PAMPs and PRRs on macrophages

provides an intracellular signal that activates the phagocyte, causing it to transition from a dormant state of readiness and slow proliferation to a state of hyperactivity, proliferation, production/secretion of cytokines, and enhanced intracellular killing. PRRs on macrophages also respond to chemical distress signals from damaged or stressed cells. This allows macrophages to extend their responses beyond protection from infectious diseases to a broader role in the inflammatory response initiated from injuries or other diseases.

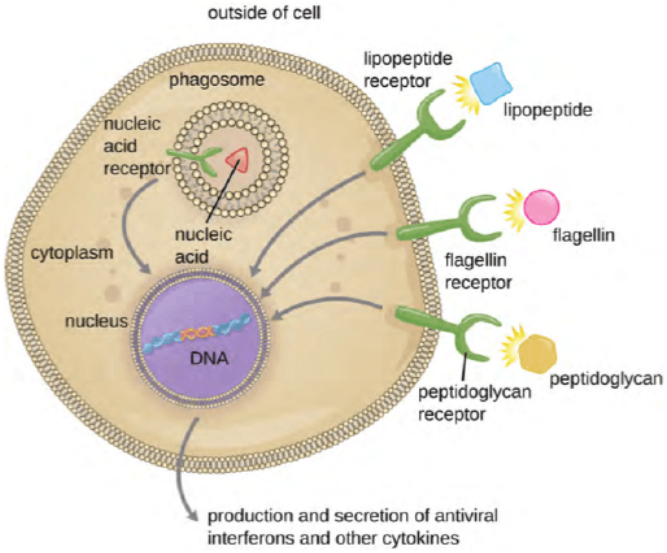



Figure 4.4.2: Phagocytic cells contain pattern recognition receptors (PRRs) capable of recognizing various pathogen-associated molecular patterns (PAMPs). These PRRs can be found on the plasma membrane or in internal phagosomes. When a PRR recognizes a PAMP, it sends a signal to the nucleus that activates genes involved in phagocytosis, cellular proliferation, production and secretion of antiviral interferons and proinflammatory cytokines, and enhanced intracellular killing.

**Exercise 4.4.2**

- Name four pathogen-associated molecular patterns (PAMPs).
- Describe the process of phagocyte activation.

## Pathogen Degradation

Once pathogen recognition and attachment occurs, the pathogen is engulfed in a vesicle and brought into the internal compartment of the phagocyte in a process called **phagocytosis** (***Figure*** 4.4.3). PRRs can aid in phagocytosis by first binding to the pathogen's surface, but phagocytes are also capable of engulfing nearby items even if they are not bound to specific receptors. To engulf the pathogen, the phagocyte forms a pseudopod that wraps around the pathogen and then pinches it off into a membrane vesicle called a **phagosome**. Acidification of the phagosome (pH decreases to the range of 4–5) provides an important early antibacterial mechanism. The phagosome containing the pathogen fuses with one or more lysosomes, forming a **phagolysosome**. Formation of the phagolysosome enhances the acidification, which is essential for activation of pH-dependent digestive lysosomal enzymes and production of hydrogen peroxide and toxic reactive oxygen species. Lysosomal enzymes such as lysozyme, phospholipase, and proteases digest the pathogen. Other enzymes are involved a respiratory burst. During the respiratory burst, phagocytes will increase their uptake and consumption of oxygen, but not for energy production. The increased oxygen consumption is focused on the production of superoxide anion, hydrogen peroxide, hydroxyl radicals, and other reactive oxygen species that are antibacterial.

In addition to the reactive oxygen species produced by the respiratory burst, reactive nitrogen compounds with cytotoxic (cell-killing) potential can also form. For example, nitric oxide can react with superoxide to form peroxynitrite, a highly reactive nitrogen compound with degrading capabilities similar to those of the reactive oxygen species. Some phagocytes even contain an internal storehouse of microbicidal defensin proteins (e.g., neutrophil granules). These destructive forces can be released into the area around the cell to degrade microbes externally. Neutrophils, especially, can be quite efficient at this secondary antimicrobial mechanism.

Once degradation is complete, leftover waste products are excreted from the cell in an exocytic vesicle. However, it is important to note that not all remains of the pathogen are excreted as waste. Macrophages and dendritic cells are also antigen-presenting cells involved in the specific adaptive immune response. These cells further process the remains of the degraded pathogen and present key antigens (specific pathogen proteins) on their cellular surface. This is an important step for stimulation of some adaptive immune responses, as will be discussed in more detail in the next chapter.

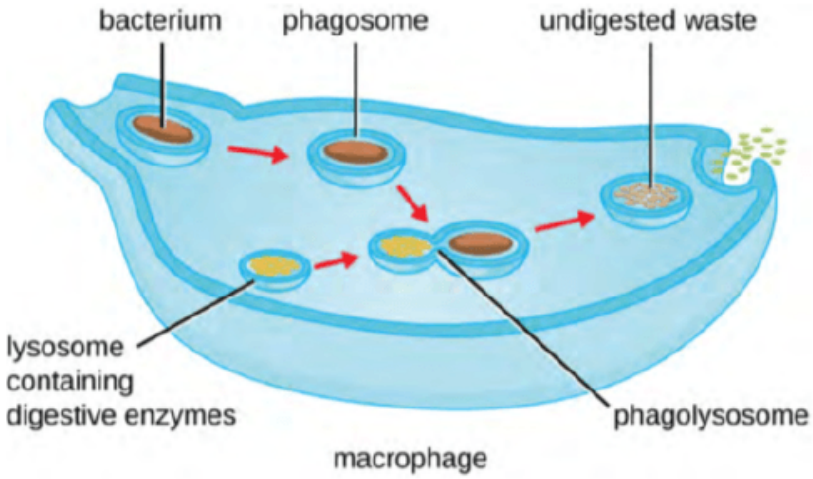



Figure 4.4.3: The stages of phagocytosis include the engulfment of a pathogen, the formation of a phagosome, the digestion of the pathogenic particle in the phagolysosome, and the expulsion of undigested materials from the cell.

## Link to Learning

Visit this link to view a phagocyte chasing and engulfing a pathogen.

## Exercise 4.4.3

- What is the difference between a phagosome and a lysosome?

## Micro Connections

**When Phagocytosis Fails**

Although phagocytosis successfully destroys many pathogens, some are able to survive and even exploit this defense mechanism to multiply in the body and cause widespread infection. Protozoans of the genusLeishmania are one example. These obligate intracellular parasites are flagellates transmitted to humans by the bite of a sand fly. Infections cause serious and sometimes disfiguring sores and ulcers in the skin and other tissues (***Figure*** 4.4.4). Worldwide, an estimated 1.3 million people are newly infected with leishmaniasis annually.[1]

Salivary peptides from the sand fly activate host macrophages at the site of their bite. The classic or alternate pathway for complement activation ensues with C3b opsonization of the parasite. Leishmania cells are phagocytosed, lose their flagella, and multiply in a form known as an amastigote (Leishman-Donovan body) within the phagolysosome. Although many other pathogens are destroyed in the phagolysosome, survival of the Leishmania amastigotes is maintained by the presence of surface lipophosphoglycan and acid phosphatase. These substances inhibit the macrophage respiratory burst and lysosomal enzymes. The parasite then multiplies inside the cell and lyses the infected macrophage, releasing the amastigotes to infect other macrophages within the same host. Should another sand fly bite an infected person, it might ingest amastigotes and then transmit them to another individual through another bite.

There are several different forms of leishmaniasis. The most common is a localized cutaneous form of the illness caused by L. tropica, which typically resolves spontaneously over time but with some significant lymphocyte infiltration and permanent scarring. A mucocutaneous form of the disease, caused by L. viannia brasilienfsis, produces lesions in the tissue of the nose and mouth and can be life threatening. A visceral form of the illness can be caused by several of the different Leishmania species. It affects various organ systems and causes abnormal enlargement of the liver and spleen. Irregular fevers, anemia, liver dysfunction, and weight loss are all signs and symptoms of visceral leishmaniasis. If left untreated, it is typically fatal.

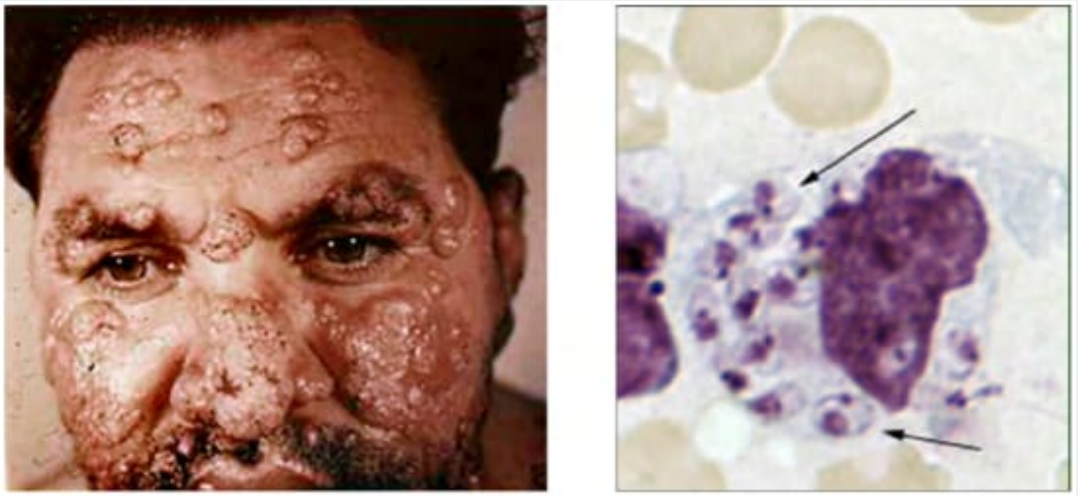



Figure 4.4.4: (a) Cutaneous leishmaniasis is a disfiguring disease caused by the intracellular flagellate *Leishmania tropica*, transmitted by the bite of a sand fly. (b) This light micrograph of a sample taken from a skin lesion shows a large cell, which is a macrophage infected with *L. tropica* amastigotes (arrows). The amastigotes have lost their flagella but their nuclei are visible. Soon the amastigotes will lyse the macrophage and be engulfed by other phagocytes, spreading the infection. (credit a: modification of work by Otis Historical Archives of "National Museum of Health & Medicine"; credit b: modification of work by Centers for Disease Control and Prevention)

## Key Concepts and Summary

- Phagocytes are cells that recognize pathogens and destroy them through phagocytosis.
- Recognition often takes place by the use of phagocyte receptors that bind molecules commonly found on pathogens, known as **pathogen-associated molecular patterns (PAMPs)**.
- The receptors that bind PAMPs are called **pattern recognition receptors**, or **PRRs**. **Toll-like receptors (TLRs)** are one type of PRR found on phagocytes.
- **Extravasation** of white blood cells from the bloodstream into infected tissue occurs through the process of **transendothelial migration**.
- Phagocytes degrade pathogens through **phagocytosis**, which involves engulfing the pathogen, killing and digesting it within a **phagolysosome**, and then excreting undigested matter.

## Footnotes

1. World Health Organization. "Leishmaniasis." 2016. http://www.who.int/mediacentre/factsheets/fs375/en/.

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# 4.5: Inflammation and Fever

**Learning Objectives**

- Identify the signs of inflammation and fever and explain why they occur
- Explain the advantages and risks posed by inflammatory responses

The inflammatory response, or **inflammation**, is triggered by a cascade of chemical mediators and cellular responses that may occur when cells are damaged and stressed or when pathogens successfully breach the physical barriers of the innate immune system. Although inflammation is typically associated with negative consequences of injury or disease, it is a necessary process insofar as it allows for recruitment of the cellular defenses needed to eliminate pathogens, remove damaged and dead cells, and initiate repair mechanisms. Excessive inflammation, however, can result in local tissue damage and, in severe cases, may even become deadly.

## Acute Inflammation

An early, if not immediate, response to tissue injury is acute inflammation. Immediately following an injury, vasoconstriction of blood vessels will occur to minimize blood loss. The amount of vasoconstriction is related to the amount of vascular injury, but it is usually brief. Vasoconstriction is followed by vasodilation and increased vascular permeability, as a direct result of the release of histamine from resident mast cells. Increased blood flow and vascular permeability can dilute toxins and bacterial products at the site of injury or infection. They also contribute to the five observable signs associated with the inflammatory response: **erythema** (redness), **edema** (swelling), heat, pain, and altered function. Vasodilation and increased vascular permeability are also associated with an influx of phagocytes at the site of injury and/or infection. This can enhance the inflammatory response because phagocytes may release proinflammatory chemicals when they are activated by cellular distress signals released from damaged cells, by PAMPs, or by opsonins on the surface of pathogens. Activation of the complement system can further enhance the inflammatory response through the production of the anaphylatoxin C5a. ***Figure*** 4.5.1 illustrates a typical case of acute inflammation at the site of a skin wound.

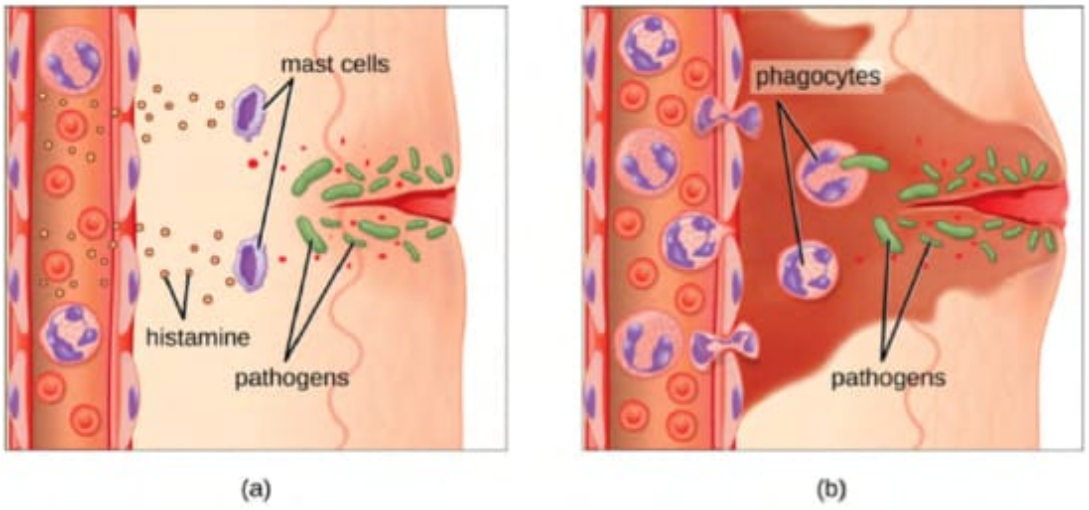



Figure 4.5.1: (a) Mast cells detect injury to nearby cells and release histamine, initiating an inflammatory response. (b) Histamine increases blood flow to the wound site, and increased vascular permeability allows fluid, proteins, phagocytes, and other immune cells to enter infected tissue. These events result in the swelling and reddening of the injured site, and the increased blood flow to the injured site causes it to feel warm. Inflammation is also associated with pain due to these events stimulating nerve pain receptors in the tissue. The interaction of phagocyte PRRs with cellular distress signals and PAMPs and opsonins on the surface of pathogens leads to the release of more proinflammatory chemicals, enhancing the inflammatory response.

During the period of inflammation, the release of bradykinin causes capillaries to remain dilated, flooding tissues with fluids and leading to edema. Increasing numbers of neutrophils are recruited to the area to fight pathogens. As the fight rages on, pus forms

from the accumulation of neutrophils, dead cells, tissue fluids, and lymph. Typically, after a few days, macrophages will help to clear out this pus. Eventually, tissue repair can begin in the wounded area.

## Chronic Inflammation

When acute inflammation is unable to clear an infectious pathogen, chronic inflammation may occur. This often results in an ongoing (and sometimes futile) lower-level battle between the host organism and the pathogen. The wounded area may heal at a superficial level, but pathogens may still be present in deeper tissues, stimulating ongoing inflammation. Additionally, chronic inflammation may be involved in the progression of degenerative neurological diseases such as Alzheimer's and Parkinson's, heart disease, and metastatic cancer.

Chronic inflammation may lead to the formation of **granulomas**, pockets of infected tissue walled off and surrounded by WBCs. Macrophages and other phagocytes wage an unsuccessful battle to eliminate the pathogens and dead cellular materials within a granuloma. One example of a disease that produces chronic inflammation is tuberculosis, which results in the formation of granulomas in lung tissues. A tubercular granuloma is called a tubercle (***Figure*** 4.5.2). Tuberculosis will be covered in more detail in Bacterial Infections of the Respiratory Tract.

Chronic inflammation is not just associated with bacterial infections. Chronic inflammation can be an important cause of tissue damage from viral infections. The extensive scarring observed with hepatitis C infections and liver cirrhosis is the result of chronic inflammation.

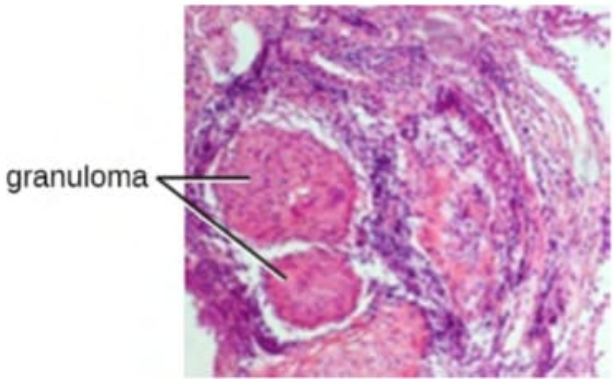



Figure 4.5.2: A tubercle is a granuloma in the lung tissue of a patient with tuberculosis. In this micrograph, white blood cells (stained purple) have walled off a pocket of tissue infected with *Mycobacterium tuberculosis*. Granulomas also occur in many other forms of disease. (credit: modification of work by Piotrowski WJ, Górski P, Duda-Szymańska J, Kwiatkowska S)

### Exercise 4.5.1

- Name the five signs of inflammation.
- Is a granuloma an acute or chronic form of inflammation? Explain.

### Micro Connections

**Chronic Edema**

In addition to granulomas, chronic inflammation can also result in long-term edema. A condition known as lymphatic filariasis (also known as elephantiasis) provides an extreme example. Lymphatic filariasis is caused by microscopic nematodes (parasitic worms) whose larvae are transmitted between human hosts by mosquitoes. Adult worms live in the lymphatic vessels, where their presence stimulates infiltration by lymphocytes, plasma cells, eosinophils, and thrombocytes (a condition known as lymphangitis). Because of the chronic nature of the illness, granulomas, fibrosis, and blocking of the lymphatic system may eventually occur. Over time, these blockages may worsen with repeated infections over decades, leading to skin thickened with edema and fibrosis. Lymph (extracellular tissue fluid) may spill out of the lymphatic areas and back into

tissues, causing extreme swelling (***Figure*** 4.5.3). Secondary bacterial infections commonly follow. Because it is a disease caused by a parasite, eosinophilia (a dramatic rise in the number of eosinophils in the blood) is characteristic of acute infection. However, this increase in antiparasite granulocytes is not sufficient to clear the infection in many cases.

Lymphatic filariasis affects an estimated 120 million people worldwide, mostly concentrated in Africa and Asia.[1] Improved sanitation and mosquito control can reduce transmission rates.



Figure 4.5.3: Elephantiasis (chronic edema) of the legs due to filariasis. (credit: modification of work by Centers for Disease Control and Prevention)

## Fever

A **fever** is an inflammatory response that extends beyond the site of infection and affects the entire body, resulting in an overall increase in body temperature. Body temperature is normally regulated and maintained by the hypothalamus, an anatomical section of the brain that functions to maintain homeostasis in the body. However, certain bacterial or viral infections can result in the production of **pyrogens**, chemicals that effectively alter the "thermostat setting" of the hypothalamus to elevate body temperature and cause fever. Pyrogens may be exogenous or endogenous. For example, the endotoxin lipopolysaccharide (LPS), produced by gram-negative bacteria, is an exogenous pyrogen that may induce the leukocytes to release endogenous pyrogens such as interleukin-1 (IL-1), IL-6, interferon-γ (IFN-γ), and tumor necrosis factor (TNF). In a cascading effect, these molecules can then lead to the release of prostaglandin E2 (PGE2) from other cells, resetting the hypothalamus to initiate fever (***Figure*** 4.5.4).

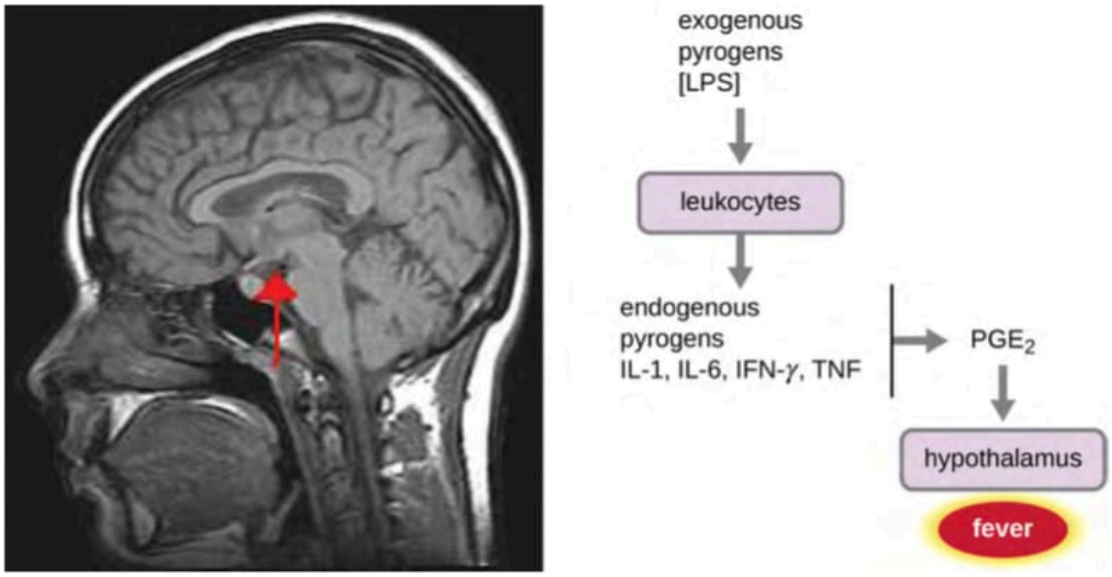



Figure 4.5.4: The role of the hypothalamus in the inflammatory response. Macrophages recognize pathogens in an area and release cytokines that trigger inflammation. The cytokines also send a signal up the vagus nerve to the hypothalamus.

Like other forms of inflammation, a fever enhances the innate immune defenses by stimulating leukocytes to kill pathogens. The rise in body temperature also may inhibit the growth of many pathogens since human pathogens are mesophiles with optimum growth occurring around 35 °C (95 °F). In addition, some studies suggest that fever may also stimulate release of iron-sequestering compounds from the liver, thereby starving out microbes that rely on iron for growth.[2]

During fever, the skin may appear pale due to vasoconstriction of the blood vessels in the skin, which is mediated by the hypothalamus to divert blood flow away from extremities, minimizing the loss of heat and raising the core temperature. The hypothalamus will also stimulate shivering of muscles, another effective mechanism of generating heat and raising the core temperature.

The **crisis phase** occurs when the fever breaks. The hypothalamus stimulates vasodilation, resulting in a return of blood flow to the skin and a subsequent release of heat from the body. The hypothalamus also stimulates sweating, which cools the skin as the sweat evaporates.

Although a low-level fever may help an individual overcome an illness, in some instances, this immune response can be too strong, causing tissue and organ damage and, in severe cases, even death. The inflammatory response to bacterial superantigens is one scenario in which a life-threatening fever may develop. Superantigens are bacterial or viral proteins that can cause an excessive activation of T cells from the specific adaptive immune defense, as well as an excessive release of cytokines that overstimulates the inflammatory response. For example, Staphylococcus aureusand Streptococcus pyogenes are capable of producing superantigens that cause toxic shock syndrome and scarlet fever, respectively. Both of these conditions can be associated with very high, life-threatening fevers in excess of 42 °C (108 °F).

## Exercise 4.5.2

- Explain the difference between exogenous and endogenous pyrogens.
- How does a fever inhibit pathogens?

## Clinical Focus

**Resolution**

Given her father's premature death, Angela's doctor suspects that she has hereditary angioedema, a genetic disorder that compromises the function of C1 inhibitor protein. Patients with this genetic abnormality may have occasional episodes of swelling in various parts of the body. In Angela's case, the swelling has occurred in the respiratory tract, leading to difficulty

breathing. Swelling may also occur in the gastrointestinal tract, causing abdominal cramping, diarrhea, and vomiting, or in the muscles of the face or limbs. This swelling may be nonresponsive to steroid treatment and is often misdiagnosed as an allergy.

Because there are three types of hereditary angioedema, the doctor orders a more specific blood test to look for levels of C1-INH, as well as a functional assay of Angela's C1 inhibitors. The results suggest that Angela has type I hereditary angioedema, which accounts for 80%–85% of all cases. This form of the disorder is caused by a deficiency in C1 esterase inhibitors, the proteins that normally help suppress activation of the complement system. When these proteins are deficient or nonfunctional, overstimulation of the system can lead to production of inflammatory anaphylatoxins, which results in swelling and fluid buildup in tissues.

There is no cure for hereditary angioedema, but timely treatment with purified and concentrated C1-INH from blood donors can be effective, preventing tragic outcomes like the one suffered by Angela's father. A number of therapeutic drugs, either currently approved or in late-stage human trials, may also be considered as options for treatment in the near future. These drugs work by inhibiting inflammatory molecules or the receptors for inflammatory molecules.

Thankfully, Angela's condition was quickly diagnosed and treated. Although she may experience additional episodes in the future, her prognosis is good and she can expect to live a relatively normal life provided she seeks treatment at the onset of symptoms.

*Go back to the previous Clinical Focus box.*

## Key Concepts and Summary

- **Inflammation** results from the collective response of chemical mediators and cellular defenses to an injury or infection.
- **Acute inflammation** is short lived and localized to the site of injury or infection. **Chronic inflammation** occurs when the inflammatory response is unsuccessful, and may result in the formation of **granulomas** (e.g., with tuberculosis) and scarring (e.g., with hepatitis C viral infections and liver cirrhosis).
- The five cardinal signs of inflammation are **erythema**, **edema**, heat, pain, and altered function. These largely result from innate responses that draw increased blood flow to the injured or infected tissue.
- **Fever** is a system-wide sign of inflammation that raises the body temperature and stimulates the immune response.
- Both inflammation and fever can be harmful if the inflammatory response is too severe.

## Footnotes

1. Centers for Disease Control and Prevention. "Parasites–Lymphatic Filiariasis." 2016. http://www.cdc.gov/parasites/lymphaticfilariasis/ gen_info/faqs.html.
2. N. Parrow et al. "Sequestration and Scavenging of Iron in Infection." *Infection and Immunity* 81 no. 10 (2013):3503–3514

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# 4.6: Review Questions

## Multiple Choice

1. Which of the following best describes the innate nonspecific immune system?
   A. a targeted and highly specific response to a single pathogen or molecule
   B. a generalized and nonspecific set of defenses against a class or group of pathogens
   C. a set of barrier mechanisms that adapts to specific pathogens after repeated exposure
   D. the production of antibody molecules against pathogens

*Answer available at the end of this section.*

2. Which of the following constantly sheds dead cells along with any microbes that may be attached to those cells?
   A. epidermis
   B. dermis
   C. hypodermis
   D. mucous membrane

*Answer available at the end of this section.*

3. Which of the following uses a particularly dense suite of tight junctions to prevent microbes from entering the underlying tissue?
   A. the mucociliary escalator
   B. the epidermis
   C. the blood-brain barrier
   D. the urethra

*Answer available at the end of this section.*

4. Which of the following serve as chemical signals between cells and stimulate a wide range of nonspecific defenses?
   A. cytokines
   B. antimicrobial peptides
   C. complement proteins
   D. antibodies

*Answer available at the end of this section.*

5. Bacteriocins and defensins are types of which of the following?
   A. leukotrienes
   B. cytokines
   C. inflammation-eliciting mediators
   D. antimicrobial peptides

*Answer available at the end of this section.*

6. Which of the following chemical mediators is secreted onto the surface of the skin?
   A. cerumen
   B. sebum
   C. gastric acid
   D. prostaglandin

*Answer available at the end of this section.*

7. Identify the complement activation pathway that is triggered by the binding of an acute-phase protein to a pathogen.
   A. classical

B. alternate
C. lectin
D. cathelicidin

*Answer available at the end of this section.*

8. Histamine, leukotrienes, prostaglandins, and bradykinin are examples of which of the following?
   A. chemical mediators primarily found in the digestive system
   B. chemical mediators that promote inflammation
   C. antimicrobial peptides found on the skin
   D. complement proteins that form MACs

*Answer available at the end of this section.*

9. White blood cells are also referred to as which of the following?
   A. platelets
   B. erythrocytes
   C. leukocytes
   D. megakaryocytes

*Answer available at the end of this section.*

10. Hematopoiesis occurs inwhich of the following?
    A. liver
    B. bone marrow
    C. kidneys
    D. central nervous system

*Answer available at the end of this section.*

11. Granulocytes are which type of cell?
    A. lymphocyte
    B. erythrocyte
    C. megakaryocyte
    D. leukocyte

*Answer available at the end of this section.*

12. PAMPs would be found on the surface of which of the following?
    A. pathogen
    B. phagocyte
    C. skin cell
    D. blood vessel wall

*Answer available at the end of this section.*

13. _____ on phagocytes bind to PAMPs on bacteria, which triggers the uptake and destruction of the bacterial pathogens?
    A. PRRs
    B. AMPs
    C. PAMPs
    D. PMNs

*Answer available at the end of this section.*

14. Which of the following best characterizes the mode of pathogen recognition for opsonin-dependent phagocytosis?
    A. Opsonins produced by a pathogen attract phagocytes through chemotaxis.
    B. A PAMP on the pathogen's surface is recognized by a phagocyte's toll-like receptors.
    C. A pathogen is first coated with a molecule such as a complement protein, which allows it to be recognized by phagocytes.

D. A pathogen is coated with a molecule such as a complement protein that immediately lyses the cell.

*Answer available at the end of this section.*

15. Which refers to swelling as a result of inflammation?
    A. erythema
    B. edema
    C. granuloma
    D. vasodilation

*Answer available at the end of this section.*

16. Which type of inflammation occurs at the site of an injury or infection?
    A. acute
    B. chronic
    C. endogenous
    D. exogenous

*Answer available at the end of this section.*

## Matching

17. Match each cell type with its description.

| | |
|---|---|
| ___natural killer cell | A. stains with basic dye methylene blue, has large amounts of histamine in granules, and facilitates allergic responses and inflammation |
| ___basophil | B. stains with acidic dye eosin, has histamine and major basic protein in granules, and facilitates responses to protozoa and helminths |
| ___macrophage | C. recognizes abnormal cells, binds to them, and releases perforin and granzyme molecules, which induce apoptosis |
| ___eosinophil | D. large agranular phagocyte that resides in tissues such as the brain and lungs |

*Answer available at the end of this section.*

18. Match each cellular defense with the infection it would most likely target.

| | |
|---|---|
| ___natural killer cell | A. virus-infected cell |
| ___neutrophil | B. tapeworm in the intestines |
| ___eosinophil | C. bacteria in a skin lesion |

*Answer available at the end of this section.*

## Fill in the Blank

19. The muscular contraction of the intestines that results in movement of material through the digestive tract is called _____.

*Answer available at the end of this section.*

20. _____ are the hair-like appendages of cells lining parts of the respiratory tract that sweep debris away from the lungs.

*Answer available at the end of this section.*

21. Secretions that bathe and moisten the interior of the intestines are produced by _____ cells.

*Answer available at the end of this section.*

22. _____ are antimicrobial peptides produced by members of the normal microbiota.

*Answer available at the end of this section.*

23. _____ is the fluid portion of a blood sample that has been drawn in the presence of an anticoagulant compound.

*Answer available at the end of this section.*

24. The process by which cells are drawn or attracted to an area by a microbe invader is known as _____.

*Answer available at the end of this section.*

25. Platelets are also called _____.

*Answer available at the end of this section.*

26. The cell in the bone marrow that gives rise to all other blood cell types is the _____.

*Answer available at the end of this section.*

27. PMNs are another name for _____.

*Answer available at the end of this section.*

28. Kupffer cells residing in the liver are a type of _____.

*Answer available at the end of this section.*

29. _____ are similar to basophils, but reside in tissues rather than circulating in the blood.

*Answer available at the end of this section.*

30. _____, also known as diapedesis, refers to the exit from the bloodstream of neutrophils and other circulating leukocytes.

*Answer available at the end of this section.*

31. Toll-like receptors are examples of _____.

*Answer available at the end of this section.*

32. A(n) _____ is a walled-off area of infected tissue that exhibits chronic inflammation.

*Answer available at the end of this section.*

33. The _____ is the part of the body responsible for regulating body temperature.

*Answer available at the end of this section.*

34. Heat and redness, or _____, occur when the small blood vessels in an inflamed area dilate (open up), bringing more blood much closer to the surface of the skin.

*Answer available at the end of this section.*

## Short Answer

35. Differentiate a physical barrier from a mechanical removal mechanism and give an example of each.
36. Identify some ways that pathogens can breach the physical barriers of the innate immune system.
37. Differentiate the main activation methods of the classic, alternative, and lectin complement cascades.
38. What are the four protective outcomes of complement activation?
39. Explain the difference between plasma and the formed elements of the blood.
40. List three ways that a neutrophil can destroy an infectious bacterium.
41. Briefly summarize the events leading up to and including the process of transendothelial migration.
42. Differentiate exogenous and endogenous pyrogens, and provide an example of each.

## Critical Thinking

43. Neutrophils can sometimes kill human cells along with pathogens when they release the toxic contents of their granules into the surrounding tissue. Likewise, natural killer cells target human cells for destruction. Explain why it is advantageous for the immune system to have cells that can kill human cells as well as pathogens.
44. Refer to Figure 6.3.2. In a blood smear taken from a healthy patient, which type of leukocyte would you expect to observe in the highest numbers?
45. If a gram-negative bacterial infection reaches the bloodstream, large quantities of LPS can be released into the blood, resulting in a syndrome called septic shock. Death due to septic shock is a real danger. The overwhelming immune and inflammatory responses that occur with septic shock can cause a perilous drop in blood pressure; intravascular blood clotting; development of thrombi and emboli that block blood vessels, leading to tissue death; failure of multiple organs; and death of the patient. Identify and characterize two to three therapies that might be useful in stopping the dangerous events and outcomes of septic shock once it has begun, given what you have learned about inflammation and innate immunity in this chapter.
46. In Lubeck, Germany, in 1930, a group of 251 infants was accidentally administered a tainted vaccine for tuberculosis that contained live *Mycobacterium tuberculosis*. This vaccine was administered orally, directly exposing the infants to the deadly bacterium. Many of these infants contracted tuberculosis, and some died. However, 44 of the infants never contracted tuberculosis. Based on your knowledge of the innate immune system, what innate defenses might have inhibited M. tuberculosis enough to prevent these infants from contracting the disease?

## Answers

**Multiple Choice**
B

**Multiple Choice**
A

**Multiple Choice**
C

**Multiple Choice**
A

**Multiple Choice**
D

**Multiple Choice**
B

**Multiple Choice**
C

**Multiple Choice**
B

**Multiple Choice**
C

**Multiple Choice**
B

**Multiple Choice**
D

**Multiple Choice**
A

**Multiple Choice**
A

**Multiple Choice**
C

**Multiple Choice**
B

**Multiple Choice**
A

**Matching**
C, A, D, B

**Matching**
A, C, B

**Fill in the Blank**
peristalsis

**Fill in the Blank**
cilia

**Fill in the Blank**
goblet

**Fill in the Blank**
bacteriocins

**Fill in the Blank**
plasma

**Fill in the Blank**
chemotaxis

**Fill in the Blank**
thrombocytes

**Fill in the Blank**
pluripotent hematopoietic stem cell (HSC)

**Fill in the Blank**
neutrophils

**Fill in the Blank**
macrophage

**Fill in the Blank**
mast cells

**Fill in the Blank**
extravasation

**Fill in the Blank**
pattern-recognition receptors (PRRs)

**Fill in the Blank**
granuloma

**Fill in the Blank**
hypothalamus

**Fill in the Blank**
erythema

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# 5: ADAPTIVE SPECIFIC HOST DEFENSES

People living in developed nations and born in the 1960s or later may have difficulty understanding the once heavy burden of devastating infectious diseases. For example, smallpox, a deadly viral disease, once destroyed entire civilizations but has since been eradicated. Thanks to the vaccination efforts by multiple groups, including the World Health Organization, Rotary International, and the United Nations Children's Fund (UNICEF), smallpox has not been diagnosed in a patient since 1977. Polio is another excellent example. This crippling viral disease paralyzed patients, who were often kept alive in "iron lung wards" as recently as the 1950s. Today, vaccination against polio has nearly eradicated the disease. Vaccines have also reduced the prevalence of once-common infectious diseases such as chickenpox, German measles, measles, mumps, and whooping cough. The success of these and other vaccines is due to the very specific and adaptive host defenses that are the focus of this chapter.

mindtouch.png

*Forum of Fargo-Moorhead ile photo of an iron lung ward during the 1940s that were prevalent in U.S. hospitals.*

Innate Nonspecific Host Defenses described innate immunity against microbial pathogens. Higher animals, such as humans, also possess an adaptive immune defense, which is highly specific for individual microbial pathogens. This specific adaptive immunity is acquired through active infection or vaccination and serves as an important defense against pathogens that evade the defenses of innate immunity.

## Chapter Outline


5.1: Overview of Specific Adaptive Immunity

5.2: Major Histocompatibility Complexes and Antigen- Presenting Cells

5.3: T Lymphocytes and Cellular Immunity

5.4: B Lymphocytes and Humoral Immunity

5.5: Vaccines

5.6: Review Questions



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# 5.1: Overview of Specific Adaptive Immunity

## Learning Objectives

- Define memory, primary response, secondary response, and specificity
- Distinguish between humoral and cellular immunity
- Differentiate between antigens, epitopes, and haptens
- Describe the structure and function of antibodies and distinguish between the different classes of antibodies

**Adaptive immunity** is defined by two important characteristics: **specificity** and **memory**. Specificity refers to the adaptive immune system's ability to target specific pathogens, and memory refers to its ability to quickly respond to pathogens to which it has previously been exposed. For example, when an individual recovers from chickenpox, the body develops a memory of the infection that will specifically protect it from the causative agent, the varicella-zoster virus, if it is exposed to the virus again later.

Specificity and memory are achieved by essentially programming certain cells involved in the immune response to respond rapidly to subsequent exposures of the pathogen. This programming occurs as a result of the first exposure to a pathogen or vaccine, which triggers a **primary response**. Subsequent exposures result in a **secondary response** that is faster and stronger as a result of the body's memory of the first exposure (***Figure*** 5.1.1). This secondary response, however, is specific to the pathogen in question. For example, exposure to one virus (e.g., varicella-zoster virus) will not provide protection against other viral diseases (e.g., measles, mumps, or polio).

Adaptive specific immunity involves the actions of two distinct cell types: **B lymphocytes** (**B cells**) and **T lymphocytes** (**T cells**). Although B cells and T cells arise from a common hematopoietic stem cell differentiation pathway (see Figure 6.3.1), their sites of maturation and their roles in adaptive immunity are very different.

B cells mature in the bone marrow and are responsible for the production of glycoproteins called **antibodies**, or **immunoglobulins**. Antibodies are involved in the body's defense against pathogens and toxins in the extracellular environment. Mechanisms of adaptive specific immunity that involve B cells and antibody production are referred to as **humoral immunity**. The maturation of T cells occurs in the thymus. T cells function as the central orchestrator of both innate and adaptive immune responses. They are also responsible for destruction of cells infected with intracellular pathogens. The targeting and destruction of intracellular pathogens by T cells is called cell-mediated immunity, or **cellular immunity**.

## Clinical Focus

**Part 1**

Olivia, a one-year old infant, is brought to the emergency room by her parents, who report her symptoms: excessive crying, irritability, sensitivity to light, unusual lethargy, and vomiting. A physician feels swollen lymph nodes in Olivia's throat and armpits. In addition, the area of the abdomen over the spleen is swollen and tender.

- What do these symptoms suggest?
- What tests might be ordered to try to diagnose the problem?

*Jump to the next Clinical Focus box.*

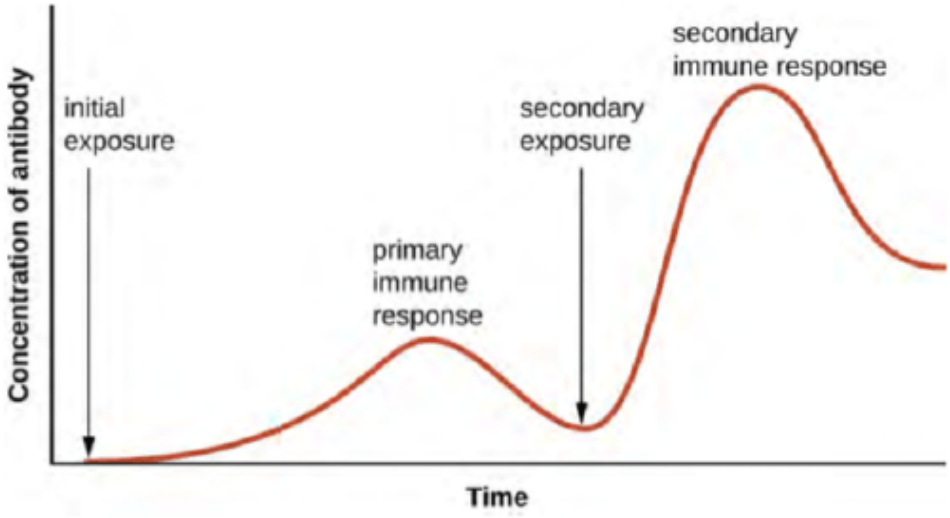



Figure 5.1.1: This graph illustrates the primary and secondary immune responses related to antibody production after an initial and secondary exposure to an antigen. Notice that the secondary response is faster and provides a much higher concentration of antibody.

**Exercise 5.1.1**

- List the two defining characteristics of adaptive immunity.
- Explain the difference between a primary and secondary immune response.
- How do humoral and cellular immunity differ?

## Antigens

Activation of the adaptive immune defenses is triggered by pathogen-specific molecular structures called **antigens**. Antigens are similar to the pathogen-associated molecular patterns (PAMPs) discussed in Pathogen Recognition and Phagocytosis; however, whereas PAMPs are molecular structures found on numerous pathogens, antigens are unique to a specific pathogen. The antigens that stimulate adaptive immunity to chickenpox, for example, are unique to the varicella-zoster virus but significantly different from the antigens associated with other viral pathogens.

The term *antigen* was initially used to describe molecules that stimulate the production of antibodies; in fact, the term comes from a combination of the words antibody and generator, and a molecule that stimulates antibody production is said to be **antigenic**. However, the role of antigens is not limited to humoral immunity and the production of antibodies; antigens also play an essential role in stimulating cellular immunity, and for this reason antigens are sometimes more accurately referred to as **immunogens**. In this text, however, we will typically refer to them as antigens.

Pathogens possess a variety of structures that may contain antigens. For example, antigens from bacterial cells may be associated with their capsules, cell walls, fimbriae, flagella, or pili. Bacterial antigens may also be associated with extracellular toxins and enzymes that they secrete. Viruses possess a variety of antigens associated with their capsids, envelopes, and the spike structures they use for attachment to cells.

Antigens may belong to any number of molecular classes, including carbohydrates, lipids, nucleic acids, proteins, and combinations of these molecules. Antigens of different classes vary in their ability to stimulate adaptive immune defenses as well as in the type of response they stimulate (humoral or cellular). The structural complexity of an antigenic molecule is an important factor in its antigenic potential. In general, more complex molecules are more effective as antigens. For example, the three-dimensional complex structure of proteins make them the most effective and potent antigens, capable of stimulating both humoral and cellular immunity. In comparison, carbohydrates are less complex in structure and therefore less effective as antigens; they can only stimulate humoral immune defenses. Lipids and nucleic acids are the least antigenic molecules, and in some cases may only become antigenic when combined with proteins or carbohydrates to form glycolipids, lipoproteins, or nucleoproteins.

One reason the three-dimensional complexity of antigens is so important is that antibodies and T cells do not recognize and interact with an entire antigen but with smaller exposed regions on the surface of antigens called **epitopes**. A single antigen may possess several different epitopes (***Figure*** 5.1.2), and different antibodies may bind to different epitopes on the same antigen (***Figure*** 5.1.3). For example, the bacterial flagellum is a large, complex protein structure that can possess hundreds or even thousands of epitopes with unique three-dimensional structures. Moreover, flagella from different bacterial species (or even strains of the same species) contain unique epitopes that can only be bound by specific antibodies.

An antigen's size is another important factor in its antigenic potential. Whereas large antigenic structures like flagella possess multiple epitopes, some molecules are too small to be antigenic by themselves. Such molecules, calledhaptens, are essentially free epitopes that are not part of the complex three-dimensional structure of a larger antigen. For a **hapten** to become antigenic, it must first attach to a larger carrier molecule (usually a protein) to produce a conjugate antigen. The hapten-specific antibodies produced in response to the conjugate antigen are then able to interact with unconjugated free hapten molecules. Haptens are not known to be associated with any specific pathogens, but they are responsible for some allergic responses. For example, the hapten urushiol, a molecule found in the oil of plants that cause poison ivy, causes an immune response that can result in a severe rash (called contact dermatitis). Similarly, the hapten penicillin can cause allergic reactions to drugs in the penicillin class.

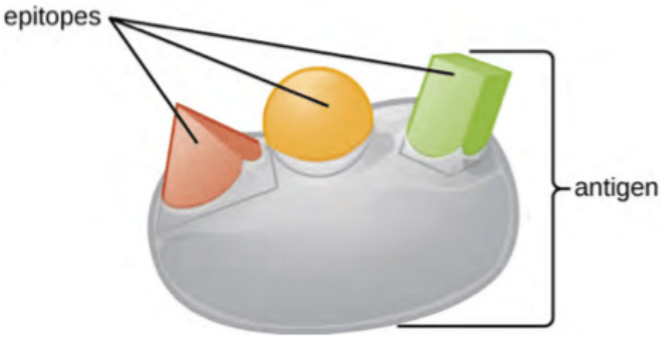



Figure 5.1.2: An antigen is a macromolecule that reacts with components of the immune system. A given antigen may contain several motifs that are recognized by immune cells.

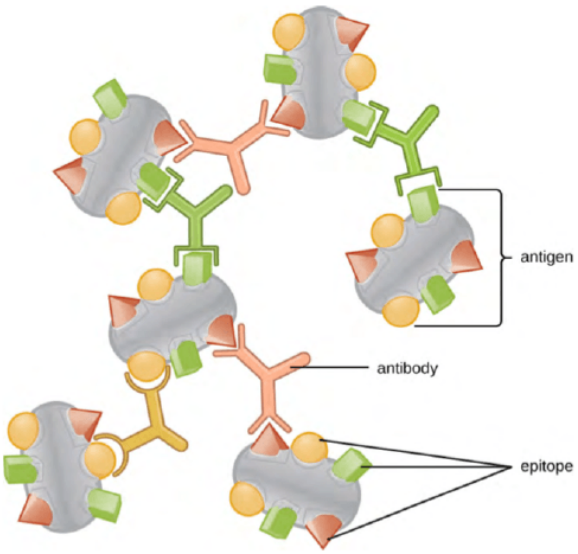



Figure 5.1.3: A typical protein antigen has multiple epitopes, shown by the ability of three different antibodies to bind to different epitopes of the same antigen.

## Exercise 5.1.2

- What is the difference between an antigen and an epitope?
- What factors affect an antigen's antigenic potential?
- Why are haptens typically not antigenic, and how do they become antigenic?

# Antibodies

Antibodies (also called immunoglobulins) are glycoproteins that are present in both the blood and tissue fluids. The basic structure of an antibody monomer consists of four protein chains held together by disulfide bonds (***Figure*** 5.1.4). A disulfide bond is a covalent bond between the sulfhydryl R groups found on two cysteine amino acids. The two largest chains are identical to each other and are called the **heavy chains**. The two smaller chains are also identical to each other and are called the **light chains**. Joined together, the heavy and light chains form a basic Y- shaped structure.

The two 'arms' of the Y-shaped antibody molecule are known as the **Fab region**, for "fragment of antigen binding." The far end of the Fab region is the variable region, which serves as the site of antigen binding. The amino acid sequence in the variable region dictates the three-dimensional structure, and thus the specific three-dimensional epitope to which the Fab region is capable of binding. Although the epitope specificity of the Fab regions is identical for each arm of a single antibody molecule, this region displays a high degree of variability between antibodies with different epitope specificities. Binding to the Fab region is necessary for neutralization of pathogens, agglutination or aggregation of pathogens, and antibody-dependent cell-mediated cytotoxicity.

The constant region of the antibody molecule includes the trunk of the Y and lower portion of each arm of the Y. The trunk of the Y is also called the **Fc region**, for "fragment of crystallization," and is the site of complement factor binding and binding to phagocytic cells during antibody-mediated opsonization.

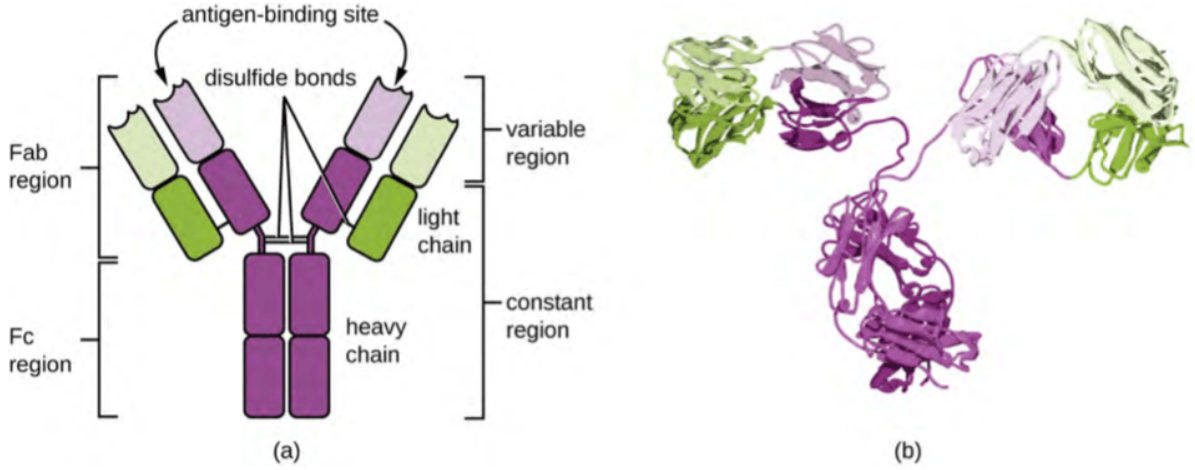



Figure 5.1.4: (a) The typical four-chain structure of a generic antibody monomer. (b) The corresponding three- dimensional structure of the antibody IgG. (credit b: modification of work by Tim Vickers)

**Exercise 5.1.3**

- Describe the different functions of the Fab region and the Fc region.

## Antibody Classes

The constant region of an antibody molecule determines its class, or isotype. The five classes of antibodies are IgG, IgM, IgA, IgD, and IgE. Each class possesses unique heavy chains designated by Greek letters γ, μ, α, δ, and ε, respectively. Antibody classes also exhibit important differences in abundance in serum, arrangement, body sites of action, functional roles, and size (***Figure*** 5.1.5).

**IgG** is a monomer that is by far the most abundant antibody in human blood, accounting for about 80% of total serum antibody. IgG penetrates efficiently into tissue spaces, and is the only antibody class with the ability to cross the placental barrier, providing passive immunity to the developing fetus during pregnancy. IgG is also the most versatile antibody class in terms of its role in the body's defense against pathogens.

**IgM** is initially produced in a monomeric membrane-bound form that serves as an antigen-binding receptor on B cells. The secreted form of IgM assembles into a pentamer with five monomers of IgM bound together by a protein structure called the

J chain. Although the location of the J chain relative to the Fc regions of the five monomers prevents IgM from performing some of the functions of IgG, the ten available Fab sites associated with a pentameric IgM make it an important antibody in the body's arsenal of defenses. IgM is the first antibody produced and secreted by B cells during the primary and secondary immune responses, making pathogen-specific IgM a valuable diagnostic marker during active or recent infections.

**IgA** accounts for about 13% of total serum antibody, and secretory IgA is the most common and abundant antibody class found in the mucus secretions that protect the mucous membranes. IgA can also be found in other secretions such as breast milk, tears, and saliva. Secretory IgA is assembled into a dimeric form with two monomers joined by a protein structure called the secretory component. One of the important functions of secretory IgA is to trap pathogens in mucus so that they can later be eliminated from the body.

Similar to IgM, **IgD** is a membrane-bound monomer found on the surface of B cells, where it serves as an antigen- binding receptor. However, IgD is not secreted by B cells, and only trace amounts are detected in serum. These trace amounts most likely come from the degradation of old B cells and the release of IgD molecules from their cytoplasmic membranes.

**IgE** is the least abundant antibody class in serum. Like IgG, it is secreted as a monomer, but its role in adaptive immunity is restricted to anti-parasitic defenses. The Fc region of IgE binds to basophils and mast cells. The Fab region of the bound IgE then interacts with specific antigen epitopes, causing the cells to release potent pro- inflammatory mediators. The inflammatory reaction resulting from the activation of mast cells and basophils aids in the defense against parasites, but this reaction is also central to allergic reactions (see Diseases of the Immune System).

The Five Immunoglobulin (Ig) Classes

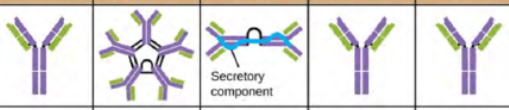
| Properties | IgG monomer | IgM pentamer | Secretory IgA dimer | IgD monomer | IgE monomer |
|---|---|---|---|---|---|
| Structure |  | | | | |
| Heavy chains | γ | μ | α | δ | ε |
| Number of antigen-binding sites | 2 | 10 | 4 | 2 | 2 |
| Molecular weight (Daltons) | 150,000 | 900,000 | 385,000 | 180,000 | 200,000 |
| Percentage of total antibody in serum | 80% | 6% | 13% (monomer) | <1% | <1% |
| Crosses placenta | yes | no | no | no | no |
| Fixes complement | yes | yes | no | no | no |
| Fc binds to | phagocytes | | | | mast cells and basophils |
| Function | Neutralization, agglutination, complement activation, opsonization, and antibody-dependent cell-mediated cytotoxicity. | Neutralization, agglutination, and complement activation. The monomer form serves as the B-cell receptor. | Neutralization and trapping of pathogens in mucus. | B-cell receptor. | Activation of basophils and mast cells against parasites and allergens. |



Figure 5.1.5

## Exercise 5.1.4

- What part of an antibody molecule determines its class?
- What class of antibody is involved in protection against parasites?
- Describe the difference in structure between IgM and IgG.

# Antigen-Antibody Interactions

Different classes of antibody play important roles in the body's defense against pathogens. These functions include neutralization of pathogens, opsonization for phagocytosis, agglutination, complement activation, and antibody- dependent cell-mediated cytotoxicity. For most of these functions, antibodies also provide an important link between adaptive specific immunity and innate nonspecific immunity.

**Neutralization** involves the binding of certain antibodies (IgG, IgM, or IgA) to epitopes on the surface of pathogens or toxins, preventing their attachment to cells. For example, Secretory IgA can bind to specific pathogens and block initial attachment to

intestinal mucosal cells. Similarly, specific antibodies can bind to certain toxins, blocking them from attaching to target cells and thus neutralizing their toxic effects. Viruses can be neutralized and prevented from infecting a cell by the same mechanism (***Figure*** 5.1.6).

As described in Chemical Defenses, opsonization is the coating of a pathogen with molecules, such as complement factors, C-reactive protein, and serum amyloid A, to assist in phagocyte binding to facilitate phagocytosis. IgG antibodies also serve as excellent opsonins, binding their Fab sites to specific epitopes on the surface of pathogens. Phagocytic cells such as macrophages, dendritic cells, and neutrophils have receptors on their surfaces that recognize and bind to the Fc portion of the IgG molecules; thus, IgG helps such phagocytes attach to and engulf the pathogens they have bound (***Figure*** 5.1.7).

**Agglutination** or aggregation involves the cross-linking of pathogens by antibodies to create large aggregates (***Figure*** 5.1.8). IgG has two Fab antigen-binding sites, which can bind to two separate pathogen cells, clumping them together. When multiple IgG antibodies are involved, large aggregates can develop; these aggregates are easier for the kidneys and spleen to filter from the blood and easier for phagocytes to ingest for destruction. The pentameric structure of IgM provides ten Fab binding sites per molecule, making it the most efficient antibody for agglutination.

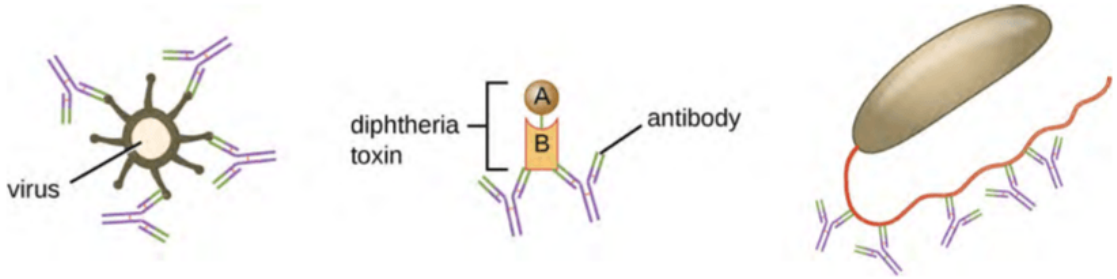



Figure 5.1.6: Neutralization involves the binding of specific antibodies to antigens found on bacteria, viruses, and toxins, preventing them from attaching to target cells.

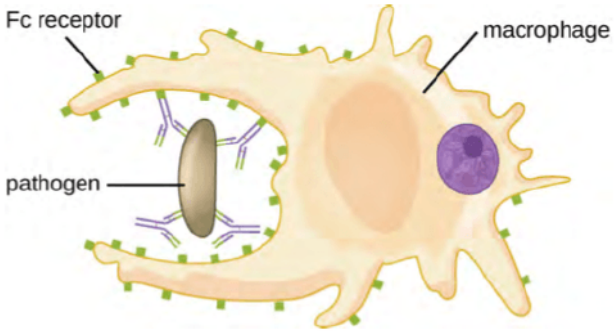



Figure 5.1.7: Antibodies serve as opsonins and inhibit infection by tagging pathogens for destruction by macrophages, dendritic cells, and neutrophils. These phagocytic cells use Fc receptors to bind to IgG-opsonized pathogens and initiate the first step of attachment before phagocytosis.

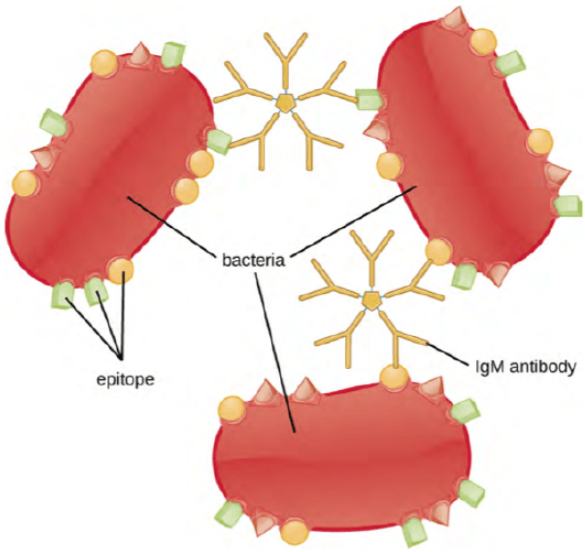



Figure 5.1.8: Antibodies, especially IgM antibodies, agglutinate bacteria by binding to epitopes on two or more bacteria simultaneously. When multiple pathogens and antibodies are present, aggregates form when the binding sites of antibodies bind with separate pathogens.

Another important function of antibodies is activation of the complement cascade. As discussed in the previous chapter, the complement system is an important component of the innate defenses, promoting the inflammatory response, recruiting phagocytes to site of infection, enhancing phagocytosis by opsonization, and killing gram- negative bacterial pathogens with the membrane attack complex (MAC). Complement activation can occur through three different pathways (see ***Figure* 17.2.2**), but the most efficient is the classical pathway, which requires the initial binding of IgG or IgM antibodies to the surface of a pathogen cell, allowing for recruitment and activation of the C1 complex.

Yet another important function of antibodies is antibody-dependent cell-mediated cytotoxicity (ADCC), which enhances killing of pathogens that are too large to be phagocytosed. This process is best characterized for natural killer cells (NK cells), as shown in ***Figure* 5.1.9**, but it can also involve macrophages and eosinophils. ADCC occurs when the Fab region of an IgG antibody binds to a large pathogen; Fc receptors on effector cells (e.g., NK cells) then bind to the Fc region of the antibody, bringing them into close proximity with the target pathogen. The effector cell then secretes powerful cytotoxins (e.g., perforin and granzymes) that kill the pathogen.

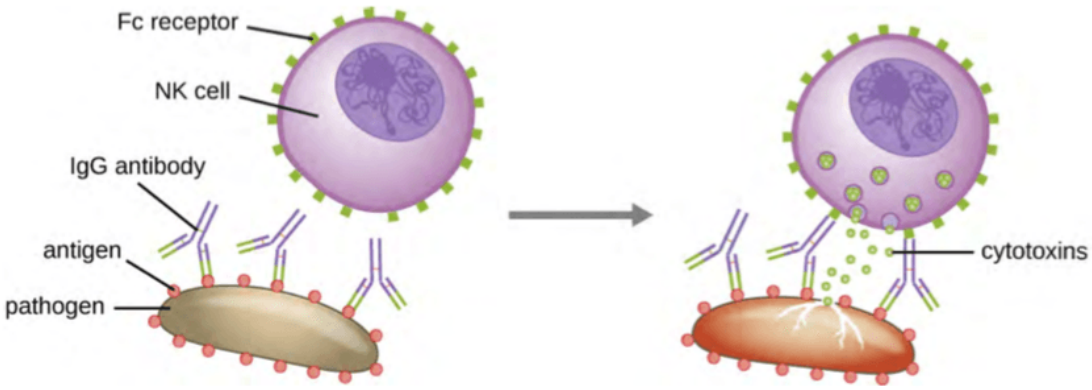



Figure 5.1.9: In this example of ADCC, antibodies bind to a large pathogenic cell that is too big for phagocytosis and then bind to Fc receptors on the membrane of a natural killer cell. This interaction brings the NK cell into close proximity, where it can kill the pathogen through release of lethal extracellular cytotoxins.

## Exercise 5.1.5

- Where is IgA normally found?
- Which class of antibody crosses the placenta, providing protection to the fetus?

- Compare the mechanisms of opsonization and antibody-dependent cell-mediated cytotoxicity.

## Key Concepts and Summary

- **Adaptive immunity** is an acquired defense against foreign pathogens that is characterized by **specificity** and **memory**. The first exposure to an antigen stimulates a **primary response**, and subsequent exposures stimulate a faster and strong **secondary response**.
- Adaptive immunity is a dual system involving **humoral immunity** (antibodies produced by B cells) and **cellular immunity** (T cells directed against intracellular pathogens).
- **Antigens**, also called **immunogens**, are molecules that activate adaptive immunity. A single antigen possesses smaller **epitopes**, each capable of inducing a specific adaptive immune response.
- An antigen's ability to stimulate an immune response depends on several factors, including its molecular class, molecular complexity, and size.
- **Antibodies** (**immunoglobulins**) are Y-shaped glycoproteins with two Fab sites for binding antigens and an Fc portion involved in complement activation and opsonization.
- The five classes of antibody are **IgM**, **IgG**, **IgA**, **IgE**, and **IgD**, each differing in size, arrangement, location within the body, and function. The five primary functions of antibodies are neutralization, opsonization, agglutination, complement activation, and antibody-dependent cell-mediated cytotoxicity (ADCC).

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# 5.2: Major Histocompatibility Complexes and Antigen-Presenting Cells

**Learning Objectives**

- Identify cells that express MHC I and/or MHC II molecules and describe the structures and cellular location of MHC I and MHC II molecules
- Identify the cells that are antigen-presenting cells
- Describe the process of antigen processing and presentation with MHC I and MHC II

As discussed in Cellular Defenses, major histocompatibility complex (MHC) molecules are expressed on the surface of healthy cells, identifying them as normal and "self" to natural killer (NK) cells. MHC molecules also play an important role in the presentation of foreign antigens, which is a critical step in the activation of T cells and thus an important mechanism of the adaptive immune system.

## Major Histocompatibility Complex Molecules

The **major histocompatibility complex (MHC)** is a collection of genes coding for MHC molecules found on the surface of all nucleated cells of the body. In humans, the MHC genes are also referred to as human leukocyte antigen (HLA) genes. Mature red blood cells, which lack a nucleus, are the only cells that do not express MHC molecules on their surface.

There are two classes of MHC molecules involved in adaptive immunity, MHC I and MHC II (***Figure*** 5.2.1). **MHC I** molecules are found on all nucleated cells; they present normal self-antigens as well as abnormal or nonself pathogens to the effector T cells involved in cellular immunity. In contrast, **MHC II** molecules are only found on macrophages, dendritic cells, and B cells; they present abnormal or nonself pathogen antigens for the initial activation of T cells.

Both types of MHC molecules are transmembrane glycoproteins that assemble as dimers in the cytoplasmic membrane of cells, but their structures are quite different. MHC I molecules are composed of a longer α protein chain coupled with a smaller β2 microglobulin protein, and only the α chain spans the cytoplasmic membrane. The α chain of the MHC I molecule folds into three separate domains: α1, α2 and α3. MHC II molecules are composed of two protein chains (an α and a β chain) that are approximately similar in length. Both chains of the MHC II molecule possess portions that span the plasma membrane, and each chain folds into two separate domains: α1 and α2, and β1, and β2. In order to present abnormal or non-self-antigens to T cells, MHC molecules have a cleft that serves as the antigen-binding site near the "top" (or outermost) portion of the MHC-I or MHC-II dimer. For MHC I, the antigen- binding cleft is formed by the α1 and α2 domains, whereas for MHC II, the cleft is formed by the α1 and β1 domains (***Figure*** 5.2.1).

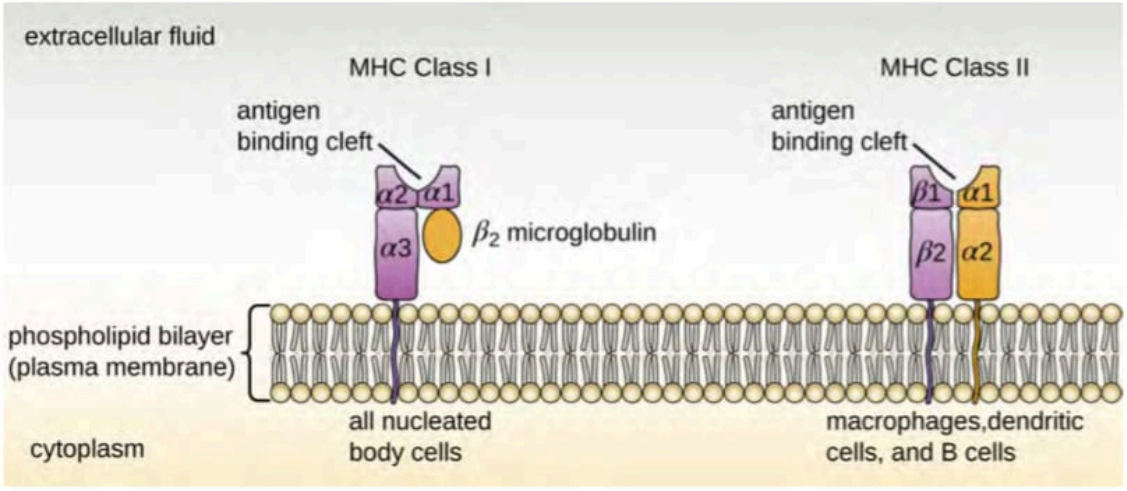



Figure 5.2.1: MHC I are found on all nucleated body cells, and MHC II are found on macrophages, dendritic cells, and B cells (along with MHC I). The antigen-binding cleft of MHC I is formed by domains $\alpha_1$ and $\alpha_2$. The antigen- binding cleft of MHC II is formed by domains $\alpha_1$ and $\beta_1$.

**Exercise 5.2.1**

- Compare the structures of the MHC I and MHC II molecules.

## Antigen-Presenting Cells (APCs)

All nucleated cells in the body have mechanisms for processing and presenting antigens in association with MHC molecules. This signals the immune system, indicating whether the cell is normal and healthy or infected with an intracellular pathogen. However, only macrophages, dendritic cells, and B cells have the ability to present antigens specifically for the purpose of activating T cells; for this reason, these types of cells are sometimes referred to **asantigen-presenting cells (APCs)**.

While all APCs play a similar role in adaptive immunity, there are some important differences to consider. Macrophages and dendritic cells are phagocytes that ingest and kill pathogens that penetrate the first-line barriers (i.e., skin and mucous membranes). B cells, on the other hand, do not function as phagocytes but play a primary role in the production and secretion of antibodies. In addition, whereas macrophages and dendritic cells recognize pathogens through nonspecific receptor interactions (e.g., PAMPs, toll-like receptors, and receptors for opsonizing complement or antibody), B cells interact with foreign pathogens or their free antigens using antigen-specific immunoglobulin as receptors (monomeric IgD and IgM). When the immunoglobulin receptors bind to an antigen, the B cell internalizes the antigen by endocytosis before processing and presentting the antigen to T cells.

## Antigen Presentation with MHC II Molecules

MHC II molecules are only found on the surface of APCs. Macrophages and dendritic cells use similar mechanisms for processing and presentation of antigens and their epitopes in association with MHC II; B cells use somewhat different mechanisms that will be described further in B Lymphocytes and Humoral Immunity. For now, we will focus on the steps of the process as they pertain to dendritic cells.

After a dendritic cell recognizes and attaches to a pathogen cell, the pathogen is internalized by phagocytosis and is initially contained within a phagosome. Lysosomes containing antimicrobial enzymes and chemicals fuse with the phagosome to create a phagolysosome, where degradation of the pathogen for antigen processing begins. Proteases (protein-degrading) are especially important in antigen processing because only protein antigen epitopes are presented to T cells by MHC II (***Figure*** 5.2.2).

APCs do not present all possible epitopes to T cells; only a selection of the most antigenic or immunodominant epitopes are presented. The mechanism by which epitopes are selected for processing and presentation by an APC is complicated and not well understood; however, once the most antigenic, immunodominant epitopes have been processed, they associate within the antigen-binding cleft of MHC II molecules and are translocated to the cell surface of the dendritic cell for presentation to T cells.

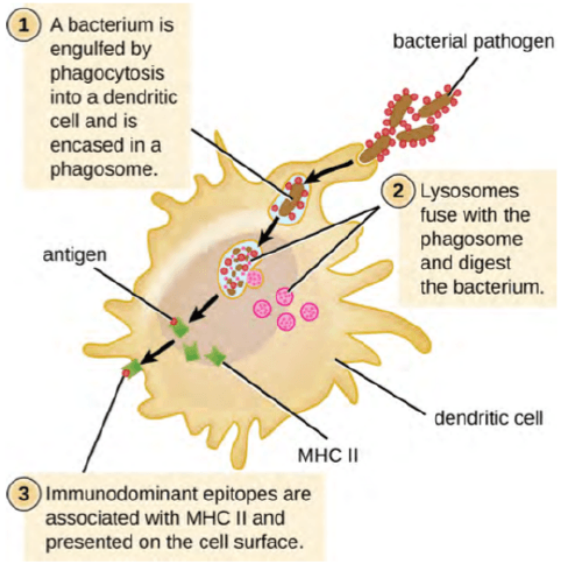



Figure 5.2.2: A dendritic cell phagocytoses a bacterial cell and brings it into a phagosome. Lysosomes fuse with the phagosome to create a phagolysosome, where antimicrobial chemicals and enzymes degrade the bacterial cell. Proteases process bacterial antigens, and the most antigenic epitopes are selected and presented on the cell's surface in conjunction with MHC II molecules. T cells recognize the presented antigens and are thus activated.

### Exercise 5.2.2

- What are the three kinds of APCs?
- What role to MHC II molecules play in antigen presentation?
- What is the role of antigen presentation in adaptive immunity?

## Antigen Presentation with MHC I Molecules

MHC I molecules, found on all normal, healthy, nucleated cells, signal to the immune system that the cell is a normal "self" cell. In a healthy cell, proteins normally found in the cytoplasm are degraded by proteasomes (enzyme complexes responsible for degradation and processing of proteins) and processed into self-antigen epitopes; these self-antigen epitopes bind within the MHC I antigen-binding cleft and are then presented on the cell surface. Immune cells, such as NK cells, recognize these self-antigens and do not target the cell for destruction. However, if a cell becomes infected with an intracellular pathogen (e.g., a virus), protein antigens specific to the pathogen are processed in the proteasomes and bind with MHC I molecules for presentation on the cell surface. This presentation of pathogen- specific antigens with MHC I signals that the infected cell must be targeted for destruction along with the pathogen.

Before elimination of infected cells can begin, APCs must first activate the T cells involved in cellular immunity. If an intracellular pathogen directly infects the cytoplasm of an APC, then the processing and presentation of antigens can occur as described (in proteasomes and on the cell surface with MHC I). However, if the intracellular pathogen does not directly infect APCs, an alternative strategy called cross-presentation is utilized. In cross-presentation, antigens are brought into the APC by mechanisms normally leading to presentation with MHC II (i.e., through phagocytosis), but the antigen is presented on an MHC I molecule for CD8 T cells. The exact mechanisms by which **cross-presentation** occur are not yet well understood, but it appears that cross-presentation is primarily a function of dendritic cells and not macrophages or B cells.

### Exercise 5.2.3

- Compare and contrast antigen processing and presentation associated with MHC I and MHC II molecules.
- What is cross-presentation, and when is it likely to occur?

## Key Concepts and Summary

- **Major histocompatibility complex (MHC)** is a collection of genes coding for glycoprotein molecules expressed on the surface of all nucleated cells.
- **MHC I** molecules are expressed on all nucleated cells and are essential for presentation of normal “self” antigens. Cells that become infected by intracellular pathogens can present foreign antigens on MHC I as well, marking the infected cell for destruction.
- **MHC II** molecules are expressed only on the surface of **antigen-presenting cells** (macrophages, dendritic cells, and B cells). Antigen presentation with MHC II is essential for the activation of T cells.
- **Antigen-presenting cells (APCs)** primarily ingest pathogens by phagocytosis, destroy them in the phagolysosomes, process the protein antigens, and select the most antigenic/immunodominant epitopes with MHC II for presentation to T cells.
- **Cross-presentation** is a mechanism of antigen presentation and T-cell activation used by dendritic cells not directly infected by the pathogen; it involves phagocytosis of the pathogen but presentation on MHC I rather than MHC II.

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# 5.3: T Lymphocytes and Cellular Immunity

**Learning Objectives**

- Describe the process of T-cell maturation and thymic selection
- Explain the genetic events that lead to diversity of T-cell receptors
- Compare and contrast the various classes and subtypes of T cells in terms of activation and function
- Explain the mechanism by which superantigens effect unregulated T-cell activation

As explained in Overview of Specific Adaptive Immunity, the antibodies involved in humoral immunity often bind pathogens and toxins before they can attach to and invade host cells. Thus, humoral immunity is primarily concerned with fighting pathogens in extracellular spaces. However, pathogens that have already gained entry to host cells are largely protected from the humoral antibody-mediated defenses. Cellular immunity, on the other hand, targets and eliminates intracellular pathogens through the actions of T lymphocytes, or T cells (***Figure*** 5.3.1). T cells also play a more central role in orchestrating the overall adaptive immune response (humoral as well as cellular) along with the cellular defenses of innate immunity.

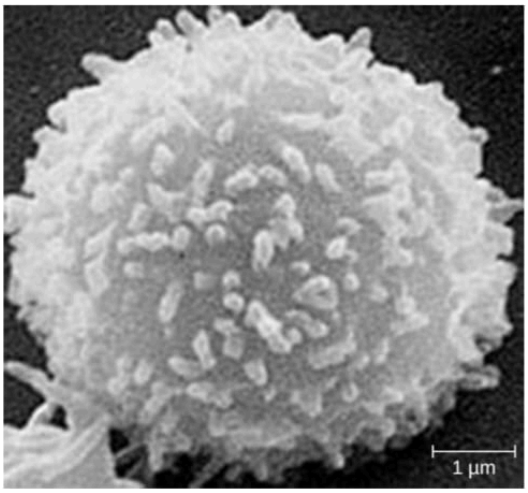



Figure 5.3.1: This scanning electron micrograph shows a T lymphocyte, which is responsible for the cell-mediated immune response. The spike-like membrane structures increase surface area, allowing for greater interaction with other cell types and their signals. (credit: modification of work by NCI)

## T Cell Production and Maturation

T cells, like all other white blood cells involved in innate and adaptive immunity, are formed from multipotent hematopoietic stem cells (HSCs) in the bone marrow (see Figure 6.3.1). However, unlike the white blood cells of innate immunity, eventual T cells differentiate first into lymphoid stem cells that then become small, immature lymphocytes, sometimes called lymphoblasts. The first steps of differentiation occur in the red marrow of bones (***Figure*** 5.3.2), after which immature T lymphocytes enter the bloodstream and travel to the thymus for the final steps of maturation (***Figure*** 5.3.2). Once in the thymus, the immature T lymphocytes are referred to as thymocytes.

The maturation of thymocytes within the thymus can be divided into tree critical steps of positive and negative selection, collectively referred to as **thymic selection**. The first step of thymic selection occurs in the cortex of the thymus and involves the development of a functional T-cell receptor (TCR) that is required for activation by APCs. Thymocytes with defective TCRs are removed by negative selection through the induction of **apoptosis** (programmed controlled cell death). The second step of thymic selection also occurs in the cortex and involves the positive selection of thymocytes that will interact appropriately with MHC molecules. Thymocytes that can interact appropriately with MHC molecules receive a positive stimulation that moves them further through the process of maturation, whereas thymocytes that do not interact appropriately are not stimulated and are eliminated by apoptosis. The third and final step of thymic selection occurs in both the cortex and medulla and involves negative selection to remove self- reacting thymocytes, those that react to self-antigens, by apoptosis. This final step is sometimes referred to as

**central tolerance** because it prevents self-reacting T cells from reaching the bloodstream and potentially causing autoimmune disease, which occurs when the immune system attacks healthy “self” cells.

Despite central tolerance, some self-reactive T cells generally escape the thymus and enter the peripheral bloodstream. Therefore, a second line of defense called **peripheral tolerance** is needed to protect against autoimmune disease. Peripheral tolerance involves mechanisms of **anergy** and inhibition of self-reactive T cells by **regulatory T cells**. Anergy refers to a state of nonresponsiveness to antigen stimulation. In the case of self-reactive T cells that escape the thymus, lack of an essential co-stimulatory signal required for activation causes anergy and prevents autoimmune activation. Regulatory T cells participate in peripheral tolerance by inhibiting the activation and function of self- reactive T cells and by secreting anti-inflammatory cytokines.

It is not completely understood what events specifically direct maturation of thymocytes into regulatory T cells. Current theories suggest the critical events may occur during the third step of thymic selection, when most self-reactive T cells are eliminated. Regulatory T cells may receive a unique signal that is below the threshold required to target them for negative selection and apoptosis. Consequently, these cells continue to mature and then exit the thymus, armed to inhibit the activation of self-reactive T cells.

It has been estimated that the three steps of thymic selection eliminate 98% of thymocytes. The remaining 2% that exit the thymus migrate through the bloodstream and lymphatic system to sites of secondary lymphoid organs/tissues, such as the lymph nodes, spleen, and tonsils (***Figure*** 5.3.3), where they await activation through the presentation of specific antigens by APCs. Until they are activated, they are known as **mature naïve T cells**.

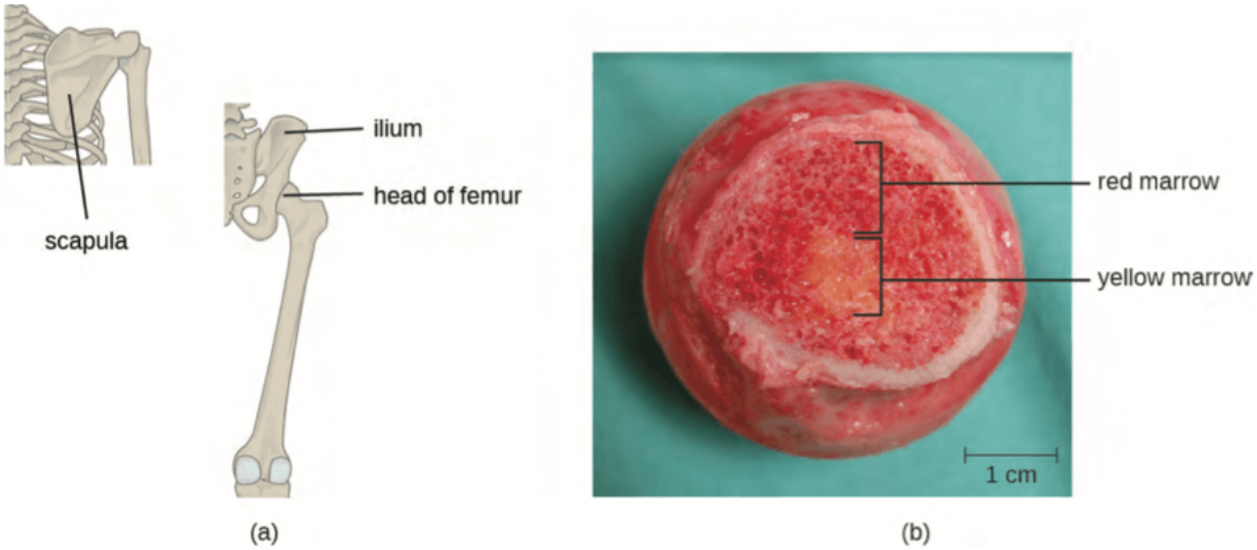



Figure 5.3.2: (a) Red bone marrow can be found in the head of the femur (thighbone) and is also present in the flat bones of the body, such as the ilium and the scapula. (b) Red bone marrow is the site of production and differentiation of many formed elements of blood, including erythrocytes, leukocytes, and platelets. The yellow bone marrow is populated primarily with adipose cells.

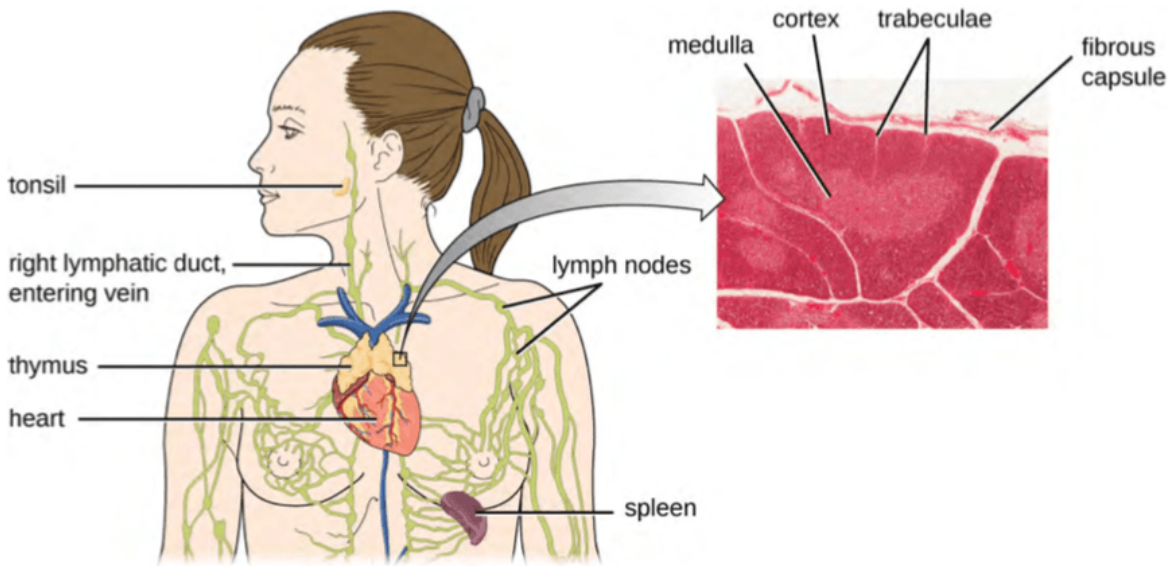



Figure 5.3.3: The thymus is a bi-lobed, H-shaped glandular organ that is located just above the heart. It is surrounded by a fibrous capsule of connective tissue. The darkly staining cortex and the lighter staining medulla of individual lobules are clearly visible in the light micrograph of the thymus of a newborn (top right, LM × 100). (credit micrograph: modification of micrograph provided by the Regents of University of Michigan Medical School © 2012)

**Exercise 5.3.1**

- What anatomical sites are involved in T cell production and maturation?
- What are the three steps involved in thymic selection?
- Why are central tolerance and peripheral tolerance important? What do they prevent?

## Classes of T Cells

T cells can be categorized into three distinct classes: helper T cells, regulatory T cells, and cytotoxic T cells. These classes are differentiated based on their expression of certain surface molecules, their mode of activation, and their functional roles in adaptive immunity (***Table*** 5.3.1).

All T cells produce **cluster of differentiation (CD) molecules**, cell surface glycoproteins that can be used to identify and distinguish between the various types of white blood cells. Although T cells can produce a variety of CD molecules, CD4 and CD8 are the two most important used for differentiation of the classes. Helper T cells and regulatory T cells are characterized by the expression of CD4 on their surface, whereas cytotoxic T cells are characterized by the expression of CD8.

Classes of T cells can also be distinguished by the specific MHC molecules and APCs with which they interact for activation. Helper T cells and regulatory T cells can only be activated by APCs presenting antigens associated with MHC II. In contrast, cytotoxic T cells recognize antigens presented in association with MHC I, either by APCs or by nucleated cells infected with an intracellular pathogen.

The different classes of T cells also play different functional roles in the immune system. **Helper T cells** serve as the central orchestrators that help activate and direct functions of humoral and cellular immunity. In addition, helper T cells enhance the pathogen-killing functions of macrophages and NK cells of innate immunity. In contrast, the primary role of regulatory T cells is to prevent undesirable and potentially damaging immune responses. Their role in peripheral tolerance, for example, protects against autoimmune disorders, as discussed earlier. Finally, **cytotoxic T cells** are the primary effector cells for cellular immunity. They recognize and target cells that have been infected by intracellular pathogens, destroying infected cells along with the pathogens inside.

*Table 5.3.1: Classes of T Cells*

| Class | Surface CD Molecules | Activation | Functions |
|---|---|---|---|
| Helper T cells | CD4 | APCs presenting antigens associated with MHC II | Orchestrate humoral and cellular immunity |
| | | | Involved in the activation of macrophages and NK cells |
| Regulatory T cells | CD4 | APCs presenting antigens associated with MHC II | Involved in peripheral tolerance and prevention of autoimmune responses |
| Cytotoxic T cells | CD8 | APCs or infected nucleated cells presenting antigens associated with MHC I | Destroy cells infected with intracellular pathogens |

**Exercise 5.3.2**

- What are the unique functions of the three classes of T cells?
- Which T cells can be activated by antigens presented by cells other than APCs?

## T-Cell Receptors

For both helper T cells and cytotoxic T cells, activation is a complex process that requires the interactions of multiple molecules and exposure to cytokines. The **T-cell receptor (TCR)** is involved in the first step of pathogen epitope recognition during the activation process.

The TCR comes from the same receptor family as the antibodies IgD and IgM, the antigen receptors on the B cell membrane surface, and thus shares common structural elements. Similar to antibodies, the TCR has a variable region and a constant region, and the variable region provides the antigen-binding site (***Figure*** 5.3.4). However, the structure of TCR is smaller and less complex than the immunoglobulin molecules (***Figure*** **18.1.4**). Whereas immunoglobulins have four peptide chains and Y-shaped structures, the TCR consists of just two peptide chains (α and β chains), both of which span the cytoplasmic membrane of the T cell.

TCRs are epitope-specific, and it has been estimated that 25 million T cells with unique epitope-binding TCRs are required to protect an individual against a wide range of microbial pathogens. Because the human genome only contains about 25,000 genes, we know that each specific TCR cannot be encoded by its own set of genes. This raises the question of how such a vast population of T cells with millions of specific TCRs can be achieved. The answer is a process called genetic rearrangement, which occurs in the thymus during the first step of thymic selection.

The genes that code for the variable regions of the TCR are divided into distinct gene segments called variable (V), diversity (D), and joining (J) segments. The genes segments associated with the α chain of the TCR consist 70 or more different Vα segments and 61 different Jα segments. The gene segments associated with the β chain of the TCR consist of 52 different $V_\beta$ segments, two different $D_\beta$ segments, and 13 different $J_\beta$ segments. During the development of the functional TCR in the thymus, genetic rearrangement in a T cell brings together one $V_\alpha$ segment and one $J_\alpha$ segment to code for the variable region of the α chain. Similarly, genetic rearrangement brings one of the $V_\beta$ segments together with one of the $D_\beta$ segments and one of the$J_\beta$ segments to code for the variable region of the β chain. All the possible combinations of rearrangements between different segments of V, D, and J provide the genetic diversity required to produce millions of TCRs with unique epitope-specific variable regions.

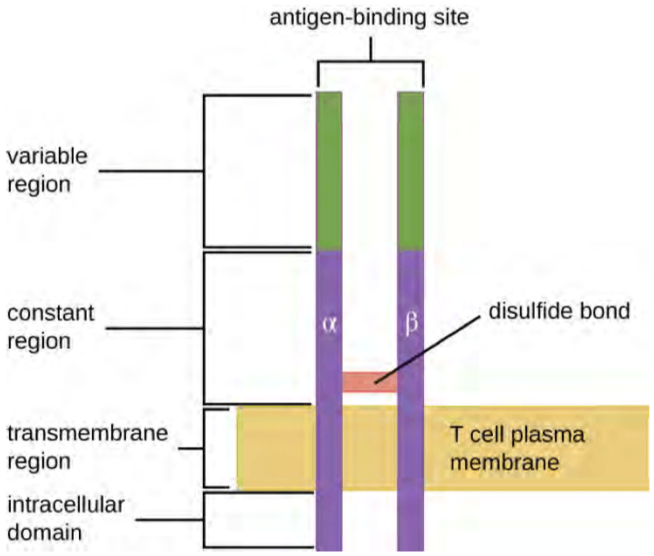



Figure 5.3.4: A T-cell receptor spans the cytoplasmic membrane and projects variable binding regions into the extracellular space to bind processed antigens associated with MHC I or MHC II molecules.

**Exercise 5.3.3**

- What are the similarities and differences between TCRs and immunoglobulins?
- What process is used to provide millions of unique TCR binding sites?

## Activation and Differentiation of Helper T Cells

Helper T cells can only be activated by APCs presenting processed foreign epitopes in association with MHC II. The first step in the activation process is TCR recognition of the specific foreign epitope presented within the MHC II antigen-binding cleft. The second step involves the interaction of CD4 on the helper T cell with a region of the MHC II molecule separate from the antigen-binding cleft. This second interaction anchors the MHC II-TCR complex and ensures that the helper T cell is recognizing both the foreign ("nonself") epitope and "self" antigen of the APC; both recognitions are required for activation of the cell. In the third step, the APC and T cell secrete cytokines that activate the helper T cell. The activated helper T cell then proliferates, dividing by mitosis to produce clonal naïve helper T cells that differentiate into subtypes with different functions (***Figure*** 5.3.5).

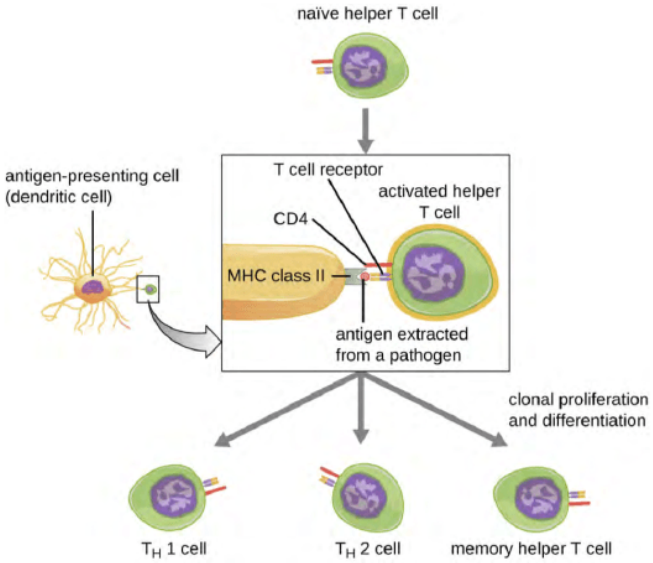



Figure 5.3.5: This illustration depicts the activation of a naïve (unactivated) helper T cell by an antigen-presenting cell and the subsequent proliferation and differentiation of the activated T cell into different subtypes.

Activated helper T cells can differentiate into one of four distinct subtypes, summarized in ***Table*** 5.3.2. The differentiation process is directed by APC-secreted cytokines. Depending on which APC-secreted cytokines interact with an activated helper T cell, the cell may differentiate into a T helper 1 ($T_H1$) cell, a T helper 2 ($T_H2$) cell, or a memory helper T cell. The two types of helper T cells are relatively short-lived effector cells, meaning that they perform various functions of the immediate immune response. In contrast, memory helper T cells are relatively long lived; they are programmed to "remember" a specific antigen or epitope in order to mount a rapid, strong, secondary response to subsequent exposures.

**$T_H1$ cells** secrete their own cytokines that are involved in stimulating and orchestrating other cells involved in adaptive and innate immunity. For example, they stimulate cytotoxic T cells, enhancing their killing of infected cells and promoting differentiation into memory cytotoxic T cells. $T_H1$ cells also stimulate macrophages and neutrophils to become more effective in their killing of intracellular bacteria. They can also stimulate NK cells to become more effective at killing target cells.

**$T_H2$ cells** play an important role in orchestrating the humoral immune response through their secretion of cytokines that activate B cells and direct B cell differentiation and antibody production. Various cytokines produced by $T_H2$ cells orchestrate antibody class switching, which allows B cells to switch between the production of IgM, IgG, IgA, and IgE as needed to carry out specific antibody functions and to provide pathogen-specific humoral immune responses.

A third subtype of helper T cells called **$T_H17$ cells** was discovered through observations that immunity to some infections is not associated with $T_H1$ or $T_H2$ cells. $T_H17$ cells and the cytokines they produce appear to be specifically responsible for the body's defense against chronic mucocutaneous infections. Patients who lack sufficient $T_H17$ cells in the mucosa (e.g., HIV patients) may be more susceptible to bacteremia and gastrointestinal infections.[1]

*Table 5.3.2: Subtypes of Helper T Cells*

| Subtype | Functions |
|---|---|
| $T_H1$ cells | Stimulate cytotoxic T cells and produce memory cytotoxic T cells |
| | Stimulate macrophages and neutrophils (PMNs) for more effective intracellular killing of pathogens |
| | Stimulate NK cells to kill more effectively |
| $T_H2$ cells | Stimulate B cell activation and differentiation into plasma cells and memory B cells |
| | Direct antibody class switching in B cells |
| $T_H17$ cells | Stimulate immunity to specific infections such as chronic mucocutaneous infections |
| Memory helper T cells | "Remember" a specific pathogen and mount a strong, rapid secondary response upon re-exposure |

# Activation and Differentiation of Cytotoxic T Cells

Cytotoxic T cells (also referred to as cytotoxic T lymphocytes, or CTLs) are activated by APCs in a three-step process similar to that of helper T cells. The key difference is that the activation of cytotoxic T cells involves recognition of an antigen presented with MHC I (as opposed to MHC II) and interaction of CD8 (as opposed to CD4) with the receptor complex. After the successful co-recognition of foreign epitope and self-antigen, the production of cytokines by the APC and the cytotoxic T cell activate clonal proliferation and differentiation. Activated cytotoxic T cells can differentiate into effector cytotoxic T cells that target pathogens for destruction or memory cells that are ready to respond to subsequent exposures.

As noted, proliferation and differentiation of cytotoxic T cells is also stimulated by cytokines secreted from $T_H1$ cells activated by the same foreign epitope. The co-stimulation that comes from these $T_H1$ cells is provided by secreted cytokines. Although it is possible for activation of cytotoxic T cells to occur without stimulation from $T_H1$ cells, the activation is not as effective or long-lasting.

Once activated, cytotoxic T cells serve as the effector cells of cellular immunity, recognizing and kill cells infected with intracellular pathogens through a mechanism very similar to that of NK cells. However, whereas NK cells recognize nonspecific signals of cell stress or abnormality, cytotoxic T cells recognize infected cells through antigen presentation of pathogen-specific epitopes associated with MHC I. Once an infected cell is recognized, the TCR of the cytotoxic T cell binds to the epitope and releases perforin and **granzymes** that destroy the infected cell (***Figure*** 5.3.6). Perforin is a protein that creates pores in the target cell, and granzymes are proteases that enter the pores and induce apoptosis. This mechanism of programmed cell death is a controlled and efficient means of destroying and removing infected cells without releasing the pathogens inside to infect neighboring cells, as might occur if the infected cells were simply lysed.

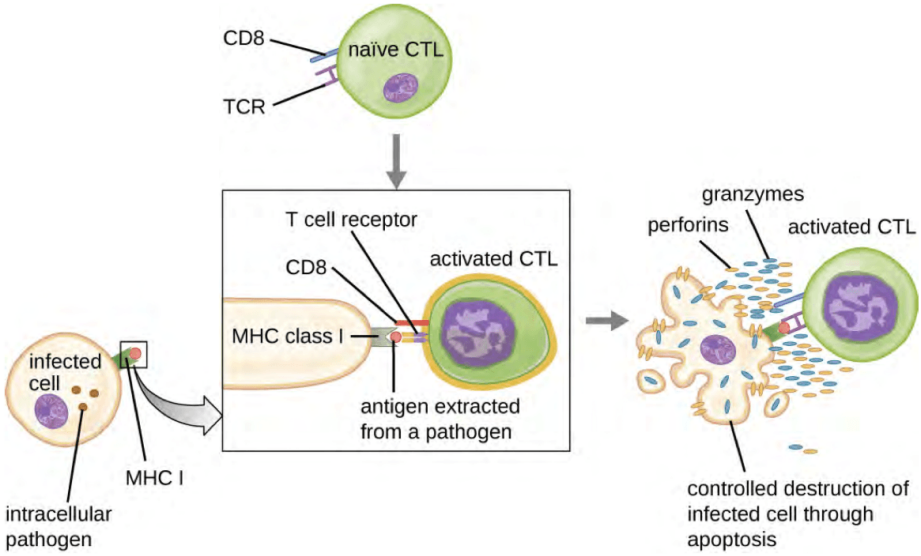



Figure 5.3.6: This figure illustrates the activation of a naïve (unactivated) cytotoxic T cell (CTL) by an antigen- presenting MHC I molecule on an infected body cell. Once activated, the CTL releases perforin and granzymes that invade the infected cell and induce controlled cell death, or apoptosis.

## Link to Learning

In this video, you can see a cytotoxic T cell inducing apoptosis in a target cell.

## Exercise 5.3.4

- Compare and contrast the activation of helper T cells and cytotoxic T cells.
- What are the different functions of helper T cell subtypes?
- What is the mechanism of CTL-mediated destruction of infected cells?

# Superantigens and Unregulated Activation of T Cells

When T cell activation is controlled and regulated, the result is a protective response that is effective in combating infections. However, if T cell activation is unregulated and excessive, the result can be a life-threatening. Certain bacterial and viral pathogens produce toxins known as superantigens (see Virulence Factors of Bacterial and Viral Pathogens) that can trigger such an unregulated response. Known bacterial superantigens include toxic shock syndrome toxin (TSST), staphylococcal enterotoxins, streptococcal pyrogenic toxins, streptococcal superantigen, and the streptococcal mitogenic exotoxin. Viruses known to produce superantigens include Epstein-Barr virus (human herpesvirus 4), cytomegalovirus (human herpesvirus 5), and others.

The mechanism of T cell activation by superantigens involves their simultaneous binding to MHC II molecules of APCs and the variable region of the TCR β chain. This binding occurs outside of the antigen-binding cleft of MHC II, so the superantigen will bridge together and activate MHC II and TCR without specific foreign epitope recognition (***Figure*** 5.3.7). The result is an excessive, uncontrolled release of cytokines, often called a cytokine storm, which stimulates an excessive inflammatory response. This can lead to a dangerous decrease in blood pressure, shock, multi- organ failure, and potentially, death.

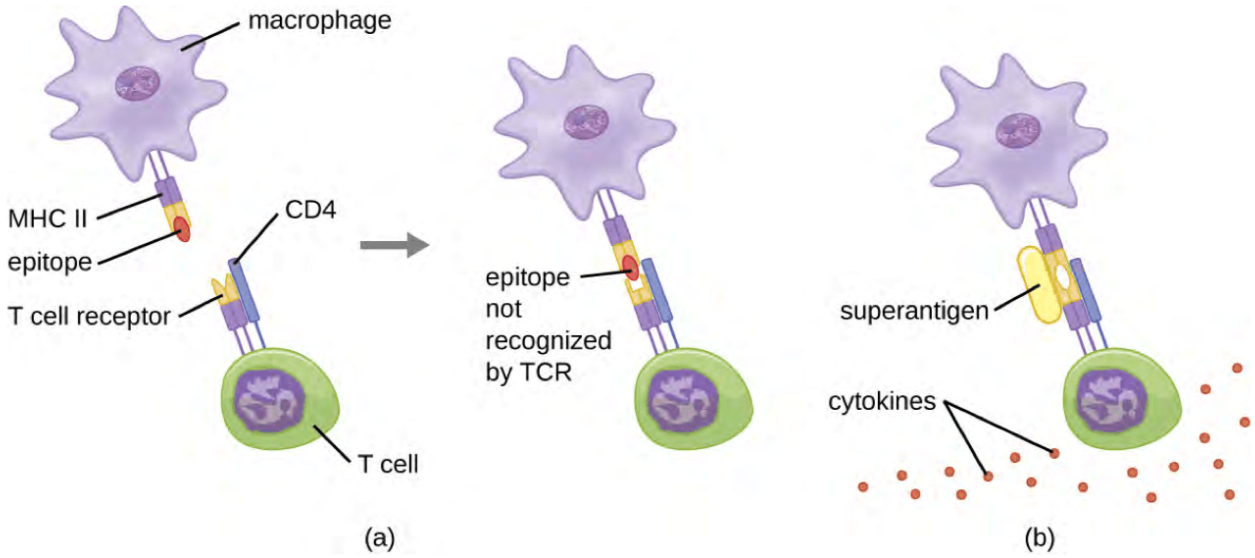



Figure 5.3.7: (a) The macrophage in this figure is presenting a foreign epitope that does not match the TCR of the T cell. Because the T cell does not recognize the epitope, it is not activated. (b) The macrophage in this figure is presenting a superantigen that is not recognized by the TCR of the T cell, yet the superantigen still is able to bridge and bind the MHC II and TCR molecules. This nonspecific, uncontrolled activation of the T cell results in an excessive release of cytokines that activate other T cells and cause excessive inflammation. (credit: modification of work by "Microbiotic"/YouTube)

## Exercise 5.3.5

- What are examples of superantigens?
- How does a superantigen activate a helper T cell?
- What effect does a superantigen have on a T cell?

## Case in Point

**Superantigens**

Melissa, an otherwise healthy 22-year-old woman, is brought to the emergency room by her concerned boyfriend. She complains of a sudden onset of high fever, vomiting, diarrhea, and muscle aches. In her initial interview, she tells the attending physician that she is on hormonal birth control and also is two days into the menstruation portion of her cycle. She is on no other medications and is not abusing any drugs or alcohol. She is not a smoker. She is not diabetic and does not currently have an infection of any kind to her knowledge.

While waiting in the emergency room, Melissa's blood pressure begins to drop dramatically and her mental state deteriorates to general confusion. The physician believes she is likely suffering from toxic shock syndrome (TSS). TSS is caused by the toxin TSST-1, a superantigen associated with *Staphylococcus aureus*, and improper tampon use is a common cause of infections leading to TSS. The superantigen inappropriately stimulates widespread T cell activation and excessive cytokine release, resulting in a massive and systemic inflammatory response that can be fatal.

Vaginal or cervical swabs may be taken to confirm the presence of the microbe, but these tests are not critical to perform based on Melissa's symptoms and medical history. The physician prescribes rehydration, supportive therapy, and antibiotics to stem the bacterial infection. She also prescribes drugs to increase Melissa's blood pressure. Melissa spends three days in the hospital undergoing treatment; in addition, her kidney function is monitored because of the high risk of kidney failure associated with TSS. After 72 hours, Melissa is well enough to be discharged to continue her recovery at home.

- In what way would antibiotic therapy help to combat a superantigen?

Clinical Focus

**Part 2**

Olivia's swollen lymph nodes, abdomen, and spleen suggest a strong immune response to a systemic infection in progress. In addition, little Olivia is reluctant to turn her head and appears to be experiencing severe neck pain. The physician orders a complete blood count, blood culture, and lumbar puncture. The cerebrospinal fluid (CSF) obtained appears cloudy and is further evaluated by Gram stain assessment and culturing for potential bacterial pathogens. The complete blood count indicates elevated numbers of white blood cells in Olivia's bloodstream. The white blood cell increases are recorded at 28.5 K/μL (normal range: 6.0–17.5 K/μL). The neutrophil percentage was recorded as 60% (normal range: 23–45%). Glucose levels in the CSF were registered at 30 mg/100 mL (normal range: 50–80 mg/100 mL). The WBC count in the CSF was 1,163/mm3(normal range: 5–20/mm3).

- Based on these results, do you have a preliminary diagnosis?
- What is a recommended treatment based on this preliminary diagnosis?

*Jump to the next Clinical Focus box. Go back to the previous Clinical Focus box.*

## Key Concepts and Summary

- Immature T lymphocytes are produced in the red bone marrow and travel to the thymus for maturation.
- **Thymic selection** is a three-step process of negative and positive selection that determines which T cells will mature and exit the thymus into the peripheral bloodstream.
- **Central tolerance** involves negative selection of self-reactive T cells in the thymus, and **peripheral tolerance** involves **anergy** and **regulatory T cells** that prevent self-reactive immune responses and autoimmunity.
- The **TCR** is similar in structure to immunoglobulins, but less complex. Millions of unique epitope-binding TCRs are encoded through a process of genetic rearrangement of V, D, and J gene segments.
- T cells can be divided into three classes—**helper T cells**, **cytotoxic T cells**, and **regulatory T cells**—based on their expression of CD4 or CD8, the MHC molecules with which they interact for activation, and their respective functions.
- Activated helper T cells differentiate into $T_H$***1***, $T_H$***2***, $T_H$***17***, or **memory T cell subtypes**. Differentiation is directed by the specific cytokines to which they are exposed. $T_H1$, $T_H2$, and $T_H17$ perform different functions related to stimulation of adaptive and innate immune defenses. Memory T cells are long-lived cells that can respond quickly to secondary exposures.
- Once activated, cytotoxic T cells target and kill cells infected with intracellular pathogens. Killing requires recognition of specific pathogen epitopes presented on the cell surface using MHC I molecules. Killing is mediated by **perforin** and **granzymes** that induce apoptosis.
- **Superantigens** are bacterial or viral proteins that cause a nonspecific activation of helper T cells, leading to an excessive release of cytokines (**cytokine storm**) and a systemic, potentially fatal inflammatory response.

## Footnotes

1. Blaschitz C., Raffatellu M. "Th17 cytokines and the gut mucosal barrier." J Clin Immunol. 2010 Mar; 30(2):196-203. doi:

10.1007/ s10875-010-9368-7.

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# 5.4: B Lymphocytes and Humoral Immunity

**Learning Objectives**

- Describe the production and maturation of B cells
- Compare the structure of B-cell receptors and T-cell receptors
- Compare T-dependent and T-independent activation of B cells
- Compare the primary and secondary antibody responses

Humoral immunity refers to mechanisms of the adaptive immune defenses that are mediated by antibodies secreted by B lymphocytes, or B cells. This section will focus on B cells and discuss their production and maturation, receptors, and mechanisms of activation.

## B Cell Production and Maturation

Like T cells, B cells are formed from multipotent hematopoietic stem cells (HSCs) in the bone marrow and follow a pathway through lymphoid stem cell and lymphoblast (see Figure 6.3.1). Unlike T cells, however, lymphoblasts destined to become B cells do not leave the bone marrow and travel to the thymus for maturation. Rather, eventual B cells continue to mature in the bone marrow.

The first step of B cell maturation is an assessment of the functionality of their antigen-binding receptors. This occurs through positive selection for B cells with normal functional receptors. A mechanism of negative selection is then used to eliminate self-reacting B cells and minimize the risk of autoimmunity. Negative selection of self-reacting B cells can involve elimination by apoptosis, editing or modification of the receptors so they are no longer self-reactive, or induction of anergy in the B cell. Immature B cells that pass the selection in the bone marrow then travel to the spleen for their final stages of maturation. There they become **naïve mature B cells**, i.e., mature B cells that have not yet been activated.

**Exercise 5.4.1**

- Compare the maturation of B cells with the maturation of T cells.

## B-Cell Receptors

Like T cells, B cells possess antigen-specific receptors with diverse specificities. Although they rely on T cells for optimum function, B cells can be activated without help from T cells. **B-cell receptors (BCRs)** for naïve mature B cells are membrane-bound monomeric forms of IgD and IgM. They have two identical heavy chains and two identical light chains connected by disulfide bonds into a basic "Y" shape (***Figure*** 5.4.1). The trunk of the Y-shaped molecule, the constant region of the two heavy chains, spans the B cell membrane. The two antigen-binding sites exposed to the exterior of the B cell are involved in the binding of specific pathogen epitopes to initiate the activation process. It is estimated that each naïve mature B cell has upwards of 100,000 BCRs on its membrane, and each of these BCRs has an identical epitope-binding specificity.

In order to be prepared to react to a wide range of microbial epitopes, B cells, like T cells, use genetic rearrangement of hundreds of gene segments to provide the necessary diversity of receptor specificities. The variable region of the BCR heavy chain is made up of V, D, and J segments, similar to the β chain of the TCR. The variable region of the BCR light chain is made up of V and J segments, similar to the α chain of the TCR. Genetic rearrangement of all possible combinations of V-J-D (heavy chain) and V-J (light chain) provides for millions of unique antigen-binding sites for the BCR and for the antibodies secreted after activation.

One important difference between BCRs and TCRs is the way they can interact with antigenic epitopes. Whereas TCRs can only interact with antigenic epitopes that are presented within the antigen-binding cleft of MHC I or MHC II, BCRs do not require antigen presentation with MHC; they can interact with epitopes on free antigens or with epitopes displayed on the surface of intact pathogens. Another important difference is that TCRs only recognize protein epitopes, whereas BCRs can recognize

epitopes associated with different molecular classes (e.g., proteins, polysaccharides, lipopolysaccharides).

Activation of B cells occurs through different mechanisms depending on the molecular class of the antigen. Activation of a B cell by a protein antigen requires the B cell to function as an APC, presenting the protein epitopes with MHC II to helper T cells. Because of their dependence on T cells for activation of B cells, protein antigens are classified as **T-dependent antigens**. In contrast, polysaccharides, lipopolysaccharides, and other nonprotein antigens are considered **T-independent antigens** because they can activate B cells without antigen processing and presentation to T cells.

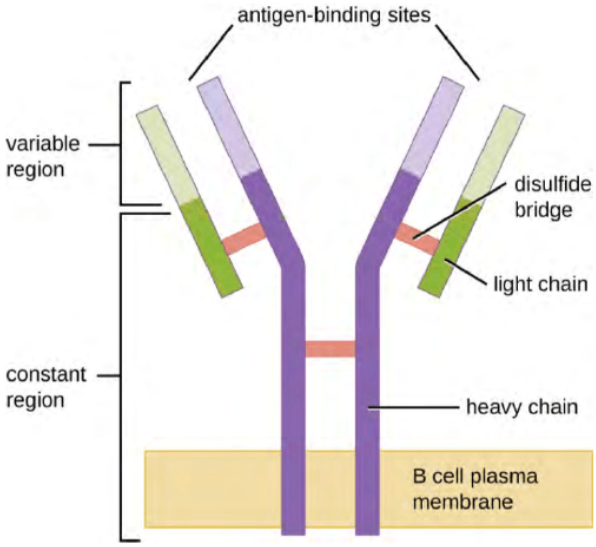



Figure 5.4.1: B-cell receptors are embedded in the membranes of B cells. The variable regions of all of the receptors on a single cell bind the same specific antigen.

Exercise 5.4.2

- What types of molecules serve as the BCR?
- What are the differences between TCRs and BCRs with respect to antigen recognition?
- Which molecule classes are T-dependent antigens and which are T-independent antigens?

## T Cell-Independent Activation of B cells

Activation of B cells without the cooperation of helper T cells is referred to as T cell-independent activation and occurs when BCRs interact with T-independent antigens. T-independent antigens (e.g., polysaccharide capsules, lipopolysaccharide) have repetitive epitope units within their structure, and this repetition allows for the cross-linkage of multiple BCRs, providing the first signal for activation (***Figure*** 5.4.2). Because T cells are not involved, the second signal has to come from other sources, such as interactions of toll-like receptors with PAMPs or interactions with factors from the complement system.

Once a B cell is activated, it undergoes clonal proliferation and daughter cells differentiate into plasma cells. **Plasma cells** are antibody factories that secrete large quantities of antibodies. After differentiation, the surface BCRs disappear and the plasma cell secretes pentameric IgM molecules that have the same antigen specificity as the BCRs (***Figure*** 5.4.2).

The T cell-independent response is short-lived and does not result in the production of memory B cells. Thus it will not result in a secondary response to subsequent exposures to T-independent antigens.

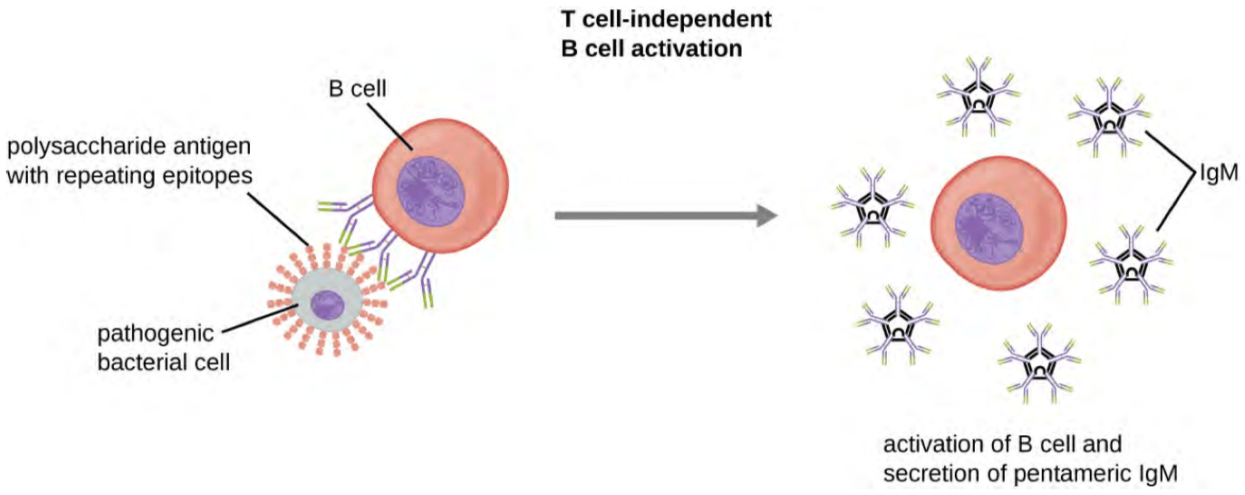



Figure 5.4.2: T-independent antigens have repeating epitopes that can induce B cell recognition and activation without involvement from T cells. A second signal, such as interaction of TLRs with PAMPs (not shown), is also required for activation of the B cell. Once activated, the B cell proliferates and differentiates into antibody-secreting plasma cells.

**Exercise 5.4.3**

- What are the two signals required for T cell-independent activation of B cells?
- What is the function of a plasma cell?

## T Cell-Dependent Activation of B cells

T cell-dependent activation of B cells is more complex than T cell-independent activation, but the resulting immune response is stronger and develops memory. T cell-dependent activation can occur either in response to free protein antigens or to protein antigens associated with an intact pathogen. Interaction between the BCRs on a naïve mature B cell and a free protein antigen stimulate internalization of the antigen, whereas interaction with antigens associated with an intact pathogen initiates the extraction of the antigen from the pathogen before internalization. Once internalized inside the B cell, the protein antigen is processed and presented with MHC II. The presented antigen is then recognized by helper T cells specific to the same antigen. The TCR of the helper T cell recognizes the foreign antigen, and the T cell's CD4 molecule interacts with MHC II on the B cell. The coordination between B cells and helper T cells that are specific to the same antigen is referred to as **linked recognition**.

Once activated by linked recognition, $T_H2$ cells produce and secrete cytokines that activate the B cell and cause proliferation into clonal daughter cells. After several rounds of proliferation, additional cytokines provided by the $T_H2$ cells stimulate the differentiation of activated B cell clones into **memory B cells**, which will quickly respond to subsequent exposures to the same protein epitope, and plasma cells that lose their membrane BCRs and initially secrete pentameric IgM (***Figure*** 5.4.3).

After initial secretion of IgM, cytokines secreted by $T_H2$ cells stimulate the plasma cells to switch from IgM production to production of IgG, IgA, or IgE. This process, called **class switching** or isotype switching, allows plasma cells cloned from the same activated B cell to produce a variety of antibody classes with the same epitope specificity. Class switching is accomplished by genetic rearrangement of gene segments encoding the constant region, which determines an antibody's class. The variable region is not changed, so the new class of antibody retains the original epitope specificity.

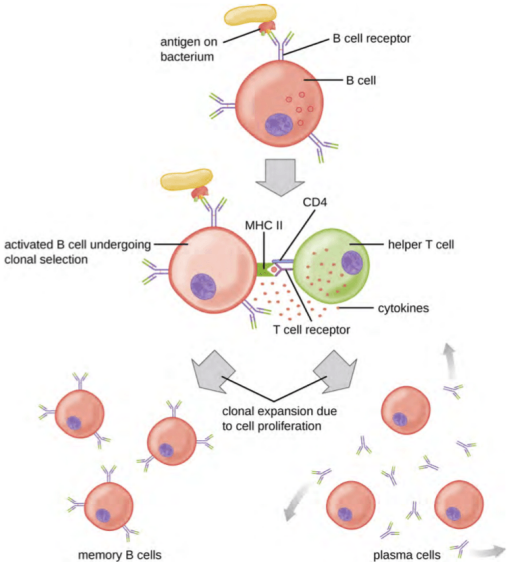



Figure 5.4.3: In T cell-dependent activation of B cells, the B cell recognizes and internalizes an antigen and presents it to a helper T cell that is specific to the same antigen. The helper T cell interacts with the antigen presented by the B cell, which activates the T cell and stimulates the release of cytokines that then activate the B cell. Activation of the B cell triggers proliferation and differentiation into B cells and plasma cells.

**Exercise 5.4.4**

- What steps are required for T cell-dependent activation of B cells?
- What is antibody class switching and why is it important?

## Primary and Secondary Responses

T cell-dependent activation of B cells plays an important role in both the primary and secondary responses associated with adaptive immunity. With the first exposure to a protein antigen, a T cell-dependent primary antibody response occurs. The initial stage of the primary response is a **lag period**, or latent period, of approximately 10 days, during which no antibody can be detected in serum. This lag period is the time required for all of the steps of the primary response, including naïve mature B cell binding of antigen with BCRs, antigen processing and presentation, helper T cell activation, B cell activation, and clonal proliferation. The end of the lag period is characterized by a rise in IgM levels in the serum, as $T_H2$ cells stimulate B cell differentiation into plasma cells. IgM levels reach their peak around 14 days after primary antigen exposure; at about this same time, $T_H2$ stimulates antibody class switching, and IgM levels in serum begin to decline. Meanwhile, levels of IgG increase until they reach a peak about three weeks into the primary response (***Figure*** 5.4.4).

During the primary response, some of the cloned B cells are differentiated into memory B cells programmed to respond to subsequent exposures. This secondary response occurs more quickly and forcefully than the primary response. The lag period is decreased to only a few days and the production of IgG is significantly higher than observed for the primary response (***Figure*** 5.4.4). In addition, the antibodies produced during the secondary response are more effective and bind with higher affinity to the targeted epitopes. Plasma cells produced during secondary responses live longer than those produced during the primary response, so levels of specific antibody remain elevated for a longer period of time.

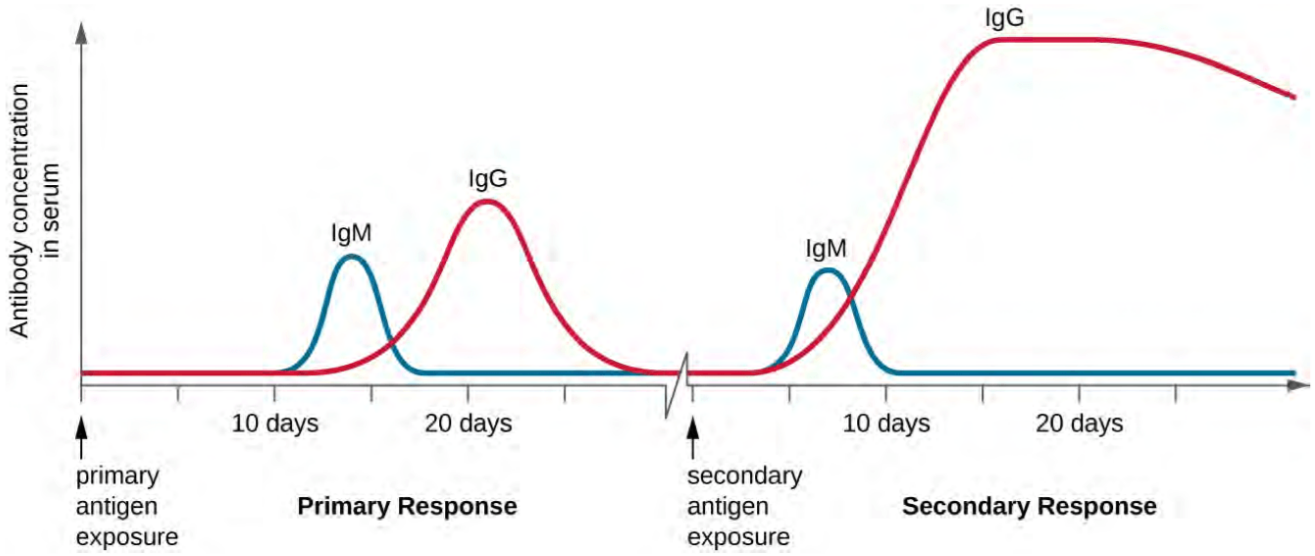



Figure 5.4.4: Compared to the primary response, the secondary antibody response occurs more quickly and produces antibody levels that are higher and more sustained. The secondary response mostly involves IgG.

**Exercise 5.4.5**

- What events occur during the lag period of the primary antibody response?
- Why do antibody levels remain elevated longer during the secondary antibody response?

## Key Concepts and Summary

- **B lymphocytes** or **B cells** produce antibodies involved in humoral immunity. B cells are produced in the bone marrow, where the initial stages of maturation occur, and travel to the spleen for final steps of maturation into naïve mature B cells.
- **B-cell receptors (BCRs)** are membrane-bound monomeric forms of IgD and IgM that bind specific antigen epitopes with their Fab antigen-binding regions. Diversity of antigen binding specificity is created by genetic rearrangement of V, D, and J segments similar to the mechanism used for TCR diversity.
- Protein antigens are called **T-dependent antigens** because they can only activate B cells with the cooperation of helper T cells. Other molecule classes do not require T cell cooperation and are called **T-independent antigens**.
- **T cell-independent activation** of B cells involves cross-linkage of BCRs by repetitive nonprotein antigen epitopes. It is characterized by the production of IgM by plasma cells and does not produce memory B cells.
- T cell-dependent activation of B cells involves processing and presentation of protein antigens to helper T cells, activation of the B cells by cytokines secreted from activated $T_H2$ cells, and plasma cells that produce different classes of antibodies as a result of **class switching**. **Memory B cells** are also produced.
- Secondary exposures to T-dependent antigens result in a secondary antibody response initiated by memory B cells. The secondary response develops more quickly and produces higher and more sustained levels of antibody with higher affinity for the specific antigen.

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# 5.5: Vaccines

**Learning Objectives**

- Compare the various kinds of artificial immunity
- Differentiate between variolation and vaccination
- Describe different types of vaccines and explain their respective advantages and disadvantages

For many diseases, prevention is the best form of treatment, and few strategies for disease prevention are as effective as vaccination. Vaccination is a form of artificial immunity. By artificially stimulating the adaptive immune defenses, a vaccine triggers memory cell production similar to that which would occur during a primary response. In so doing, the patient is able to mount a strong secondary response upon exposure to the pathogen—but without having to first suffer through an initial infection. In this section, we will explore several different kinds of artificial immunity along with various types of vaccines and the mechanisms by which they induce artificial immunity.

## Classifications of Adaptive Immunity

All forms of adaptive immunity can be described as either active or passive. **Active immunity** refers to the activation of an individual's own adaptive immune defenses, whereas **passive immunity** refers to the transfer of adaptive immune defenses from another individual or animal. Active and passive immunity can be further subdivided based on whether the protection is acquired naturally or artificially.

**Natural active immunity** is adaptive immunity that develops after natural exposure to a pathogen (***Figure*** 5.5.1). Examples would include the lifelong immunity that develops after recovery from a chickenpox or measles infection (although an acute infection is not always necessary to activate adaptive immunity). The length of time that an individual is protected can vary substantially depending upon the pathogen and antigens involved. For example, activation of adaptive immunity by protein spike structures during an intracellular viral infection can activate lifelong immunity, whereas activation by carbohydrate capsule antigens during an extracellular bacterial infection may activate shorter-term immunity.

**Natural passive immunity** involves the natural passage of antibodies from a mother to her child before and after birth. IgG is the only antibody class that can cross the placenta from mother's blood to the fetal blood supply. Placental transfer of IgG is an important passive immune defense for the infant, lasting up to six months after birth. Secretory IgA can also be transferred from mother to infant through breast milk.

**Artificial passive immunity** refers to the transfer of antibodies produced by a donor (human or animal) to another individual. This transfer of antibodies may be done as a prophylactic measure (i.e., to prevent disease after exposure to a pathogen) or as a strategy for treating an active infection. For example, artificial passive immunity is commonly used for post-exposure prophylaxis against rabies, hepatitis A, hepatitis B, and chickenpox (in high risk individuals). Active infections treated by artificial passive immunity include cytomegalovirus infections in immunocompromised patients and Ebola virus infections. In 1995, eight patients in the Democratic Republic of the Congo with active Ebola infections were treated with blood transfusions from patients who were recovering from Ebola. Only one of the eight patients died (a 12.5% mortality rate), which was much lower than the expected 80% mortality rate for Ebola in untreated patients.[1] Artificial passive immunity is also used for the treatment of diseases caused by bacterial toxins, including tetanus, botulism, and diphtheria.

Artificial active immunity is the foundation for vaccination. It involves the activation of adaptive immunity through the deliberate exposure of an individual to weakened or inactivated pathogens, or preparations consisting of key pathogen antigens.

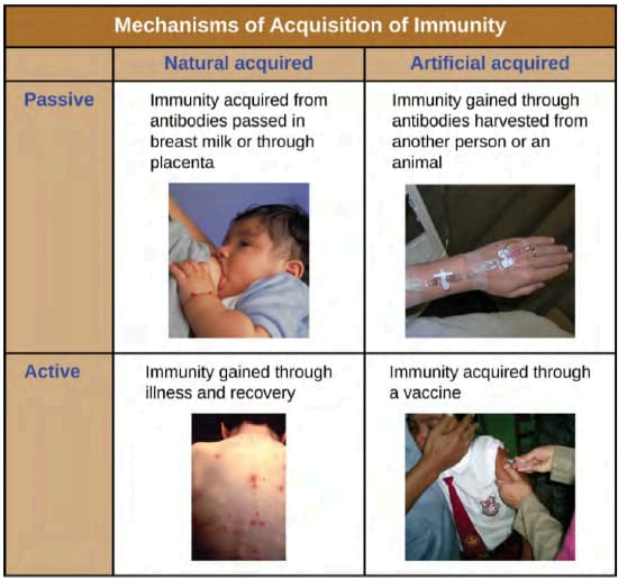



Figure 5.5.1: The four classifications of immunity. (credit top left photo: modification of work by USDA; credit top right photo: modification of work by "Michaelberry"/Wikimedia; credit bottom left photo: modification of work by Centers for Disease Control and Prevention; credit bottom right photo: modification of work by Friskila Silitonga, Indonesia, Centers for Disease Control and Prevention)

### Exercise 5.5.1

- What is the difference between active and passive immunity?
- What kind of immunity is conferred by a vaccine?

## Herd Immunity

The four kinds of immunity just described result from an individual's adaptive immune system. For any given disease, an individual may be considered immune or susceptible depending on his or her ability to mount an effective immune response upon exposure. Thus, any given population is likely to have some individuals who are immune and other individuals who are susceptible. If a population has very few susceptible individuals, even those susceptible individuals will be protected by a phenomenon called **herd immunity**. Herd immunity has nothing to do with an individual's ability to mount an effective immune response; rather, it occurs because there are too few susceptible individuals in a population for the disease to spread effectively.

Vaccination programs create herd immunity by greatly reducing the number of susceptible individuals in a population. Even if some individuals in the population are not vaccinated, as long as a certain percentage is immune (either naturally or artificially), the few susceptible individuals are unlikely to be exposed to the pathogen. However, because new individuals are constantly entering populations (for example, through birth or relocation), vaccination programs are necessary to maintain herd immunity.

### Eye on Ethics

**Vaccination: Obligation or Choice**

A growing number of parents are choosing not to vaccinate their children. They are dubbed "antivaxxers," and the majority of them believe that vaccines are a cause of autism (or other disease conditions), a link that has now been thoroughly disproven. Others object to vaccines on religious or moral grounds (e.g., the argument that Gardasil vaccination against HPV may promote sexual promiscuity), on personal ethical grounds (e.g., a conscientious objection to any medical intervention), or on political grounds (e.g., the notion that mandatory vaccinations are a violation of individual liberties).[2]

It is believed that this growing number of unvaccinated individuals has led to new outbreaks of whooping cough and measles. We would expect that herd immunity would protect those unvaccinated in our population, but herd immunity can only be maintained if enough individuals are being vaccinated.

Vaccination is clearly beneficial for public health. But from the individual parent's perspective the view can be murkier. Vaccines, like all medical interventions, have associated risks, and while the risks of vaccination may be extremely low compared to the risks of infection, parents may not always understand or accept the consensus of the medical community. Do such parents have a right to withhold vaccination from their children? Should they be allowed to put their children—and society at large—at risk?

Many governments insist on childhood vaccinations as a condition for entering public school, but it has become easy in most states to opt out of the requirement or to keep children out of the public system. Since the 1970s, West Virginia and Mississippi have had in place a stringent requirement for childhood vaccination, without exceptions, and neither state has had a case of measles since the early 1990s. California lawmakers recently passed a similar law in response to a measles outbreak in 2015, making it much more difficult for parents to opt out of vaccines if their children are attending public schools. Given this track record and renewed legislative efforts, should other states adopt similarly strict requirements?

What role should health-care providers play in promoting or enforcing universal vaccination? Studies have shown that many parents' minds can be changed in response to information delivered by health-care workers, but is it the place of health-care workers to try to persuade parents to have their children vaccinated? Some health-care providers are understandably reluctant to treat unvaccinated patients. Do they have the right to refuse service to patients who decline vaccines? Do insurance companies have the right to deny coverage to antivaxxers? These are all ethical questions that policymakers may be forced to address as more parents skirt vaccination norms.

## Variolation and Vaccination

Thousands of years ago, it was first recognized that individuals who survived a smallpox infection were immune to subsequent infections. The practice of inoculating individuals to actively protect them from smallpox appears to have originated in the 10th century in China, when the practice of **variolation** was described (***Figure*** 5.5.2). Variolation refers to the deliberate inoculation of individuals with infectious material from scabs or pustules of smallpox victims. Infectious materials were either injected into the skin or introduced through the nasal route. The infection that developed was usually milder than naturally acquired smallpox, and recovery from the milder infection provided protection against the more serious disease.

Although the majority of individuals treated by variolation developed only mild infections, the practice was not without risks. More serious and sometimes fatal infections did occur, and because smallpox was contagious, infections resulting from variolation could lead to epidemics. Even so, the practice of variolation for smallpox prevention spread to other regions, including India, Africa, and Europe.



Figure 5.5.2: Variolation for smallpox originated in the Far East and the practice later spread to Europe and Africa. This Japanese relief depicts a patient receiving a smallpox variolation from the physician Ogata Shunsaku (1748–1810).

Although variolation had been practiced for centuries, the English physician Edward Jenner (1749–1823) is generally credited with developing the modern process of vaccination. Jenner observed that milkmaids who developed cowpox, a disease similar

to smallpox but milder, were immune to the more serious smallpox. This led Jenner to hypothesize that exposure to a less virulent pathogen could provide immune protection against a more virulent pathogen, providing a safer alternative to variolation. In 1796, Jenner tested his hypothesis by obtaining infectious samples from a milkmaid's active cowpox lesion and injecting the materials into a young boy (***Figure*** 5.5.3). The boy developed a mild infection that included a low-grade fever, discomfort in his axillae (armpit) and loss of appetite. When the boy was later infected with infectious samples from smallpox lesions, he did not contract smallpox.[3] This new approach was termed **vaccination**, a name deriving from the use of cowpox (Latin vacca meaning "cow") to protect against smallpox. Today, we know that Jenner's vaccine worked because the cowpox virus is genetically and antigenically related to the Variola viruses that caused smallpox. Exposure to cowpox antigens resulted in a primary response and the production of memory cells that identical or related epitopes of Variola virus upon a later exposure to smallpox.

The success of Jenner's smallpox vaccination led other scientists to develop vaccines for other diseases. Perhaps the most notable was Louis Pasteur, who developed vaccines for rabies, cholera, and anthrax. During the $20^{th}$ and $21^{st}$ centuries, effective vaccines were developed to prevent a wide range of diseases caused by viruses (e.g., chickenpox and shingles, hepatitis, measles, mumps, polio, and yellow fever) and bacteria (e.g., diphtheria, pneumococcal pneumonia, tetanus, and whooping cough).




Figure 5.5.3: (a) A painting of Edward Jenner depicts a cow and a milkmaid in the background. (b) Lesions on a patient infected with cowpox, a zoonotic disease caused by a virus closely related to the one that causes smallpox. (credit b: modification of work by the Centers for Disease Control and Prevention)

**Exercise 5.5.2**

- What is the difference between variolation and vaccination for smallpox?
- Explain why vaccination is less risky than variolation.

## Classes of Vaccines

For a vaccine to provide protection against a disease, it must expose an individual to pathogen-specific antigens that will stimulate a protective adaptive immune response. By its very nature, this entails some risk. As with any pharmaceutical drug, vaccines have the potential to cause adverse effects. However, the ideal vaccine causes no severe adverse effects and poses no risk of contracting the disease that it is intended to prevent. Various types of vaccines have been developed with these goals in mind. These different classes of vaccines are described in the next section and summarized in ***Table*** 5.5.1.

### Live Attenuated Vaccines

**Live attenuated vaccines** expose an individual to a weakened strain of a pathogen with the goal of establishing a subclinical infection that will activate the adaptive immune defenses. Pathogens are attenuated to decrease their virulence using methods such as genetic manipulation (to eliminate key virulence factors) or long-term culturing in an unnatural host or environment (to promote mutations and decrease virulence).

By establishing an active infection, live attenuated vaccines stimulate a more comprehensive immune response than some other types of vaccines. Live attenuated vaccines activate both cellular and humoral immunity and stimulate the development of memory for long-lasting immunity. In some cases, vaccination of one individual with a live attenuated pathogen can even lead to natural transmission of the attenuated pathogen to other individuals. This can cause the other individuals to also develop an active, subclinical infection that activates their adaptive immune defenses.

Disadvantages associated with live attenuated vaccines include the challenges associated with long-term storage and transport as well as the potential for a patient to develop signs and symptoms of disease during the active infection (particularly in immunocompromised patients). There is also a risk of the attenuated pathogen reverting back to full virulence. ***Table*** $5.5.1$ lists examples live attenuated vaccines.

## Inactivated Vaccines

**Inactivated vaccines** contain whole pathogens that have been killed or inactivated with heat, chemicals, or radiation. For inactivated vaccines to be effective, the inactivation process must not affect the structure of key antigens on the pathogen.

Because the pathogen is killed or inactive, inactivated vaccines do not produce an active infection, and the resulting immune response is weaker and less comprehensive than that provoked by a live attenuated vaccine. Typically the response involves only humoral immunity, and the pathogen cannot be transmitted to other individuals. In addition, inactivated vaccines usually require higher doses and multiple boosters, possibly causing inflammatory reactions at the site of injection.

Despite these disadvantages, inactivated vaccines do have the advantages of long-term storage stability and ease of transport. Also, there is no risk of causing severe active infections. However, inactivated vaccines are not without their side effects. Table $5.5.1$ lists examples of inactivated vaccines.

## Subunit Vaccines

Whereas live attenuated and inactive vaccines expose an individual to a weakened or dead pathogen, **subunit vaccines** only expose the patient to the key antigens of a pathogen—not whole cells or viruses. Subunit vaccines can be produced either by chemically degrading a pathogen and isolating its key antigens or by producing the antigens through genetic engineering. Because these vaccines contain only the essential antigens of a pathogen, the risk of side effects is relatively low. ***Table*** $5.5.1$ lists examples of subunit vaccines.

## Toxoid Vaccines

Like subunit vaccines, **toxoid vaccines** do not introduce a whole pathogen to the patient; they contain inactivated bacterial toxins, called toxoids. Toxoid vaccines are used to prevent diseases in which bacterial toxins play an important role in pathogenesis. These vaccines activate humoral immunity that neutralizes the toxins. ***Table*** $5.5.1$ lists examples of toxoid vaccines.

## Conjugate Vaccines

A **conjugate vaccine** is a type of subunit vaccine that consists of a protein conjugated to a capsule polysaccharide. Conjugate vaccines have been developed to enhance the efficacy of subunit vaccines against pathogens that have protective polysaccharide capsules that help them evade phagocytosis, causing invasive infections that can lead to meningitis and other serious conditions. The subunit vaccines against these pathogens introduce T-independent capsular polysaccharide antigens that result in the production of antibodies that can opsonize the capsule and thus combat the infection; however, children under the age of two years do not respond effectively to these vaccines. Children do respond effectively when vaccinated with the conjugate vaccine, in which a protein with T-dependent antigens is conjugated to the capsule polysaccharide. The conjugated protein-polysaccharide antigen stimulates production of antibodies against both the protein and the capsule polysaccharide. ***Table*** $5.5.1$ lists examples of conjugate vaccines.

*Table 5.5.1: Classes of Vaccines*

| Class | Description | Advantages | Disadvantages | Examples |
|---|---|---|---|---|
| Live attenuated | Weakened strain of whole pathogen | Cellular and humoral immunity | Difficult to store and transport | Chickenpox, German measles, measles, mumps, tuberculosis, typhoid fever, yellow fever |
| | | Long-lasting immunity | Risk of infection in immunocompromised patients | |
| | | Transmission to contacts | Risk of reversion | |
| Inactivated | Whole pathogen killed or inactivated with heat, chemicals, or radiation | Ease of storage and transport | Weaker immunity (humoral only) | Cholera, hepatitis A, influenza, plague, rabies |
| | | No risk of severe active infection | Higher doses and more boosters required | |
| Subunit | Immunogenic antigens | Lower risk of side effects | Limited longevity | Anthrax, hepatitis B, influenza, meningitis, papillomavirus, pneumococcal pneumonia, whooping cough |
| | | | Multiple doses required | |
| | | | No protection against antigenic variation | |
| Toxoid | Inactivated bacterial toxin | Humoral immunity to neutralize toxin | Does not prevent infection | Botulism, diphtheria, pertussis, tetanus |
| Conjugate | Capsule polysaccharide conjugated to protein | T-dependent response to capsule | Costly to produce | Meningitis (*Haemophilus influenzae*, *Streptococcus pneumoniae*, *Neisseria meningitides*) |
| | | | No protection against antigenic variation | |
| | | Better response in young children | May interfere with other vaccines | |

## Exercise 5.5.3

- What is the risk associated with a live attenuated vaccine?
- Why is a conjugated vaccine necessary in some cases?

## Micro Connections

**DNA Vaccines**

DNA vaccines represent a relatively new and promising approach to vaccination. A DNA vaccine is produced by incorporating genes for antigens into a recombinant plasmid vaccine. Introduction of the DNA vaccine into a patient leads to uptake of the recombinant plasmid by some of the patient's cells, followed by transcription and translation of antigens and presentation of these antigens with MHC I to activate adaptive immunity. This results in the stimulation of both humoral and cellular immunity without the risk of active disease associated with live attenuated vaccines.

Although most DNA vaccines for humans are still in development, it is likely that they will become more prevalent in the near future as researchers are working on engineering DNA vaccines that will activate adaptive immunity against several different pathogens at once. First-generation DNA vaccines tested in the 1990s looked promising in animal models but were disappointing when tested in human subjects. Poor cellular uptake of the DNA plasmids was one of the major problems impacting their efficacy. Trials of second-generation DNA vaccines have been more promising thanks to new techniques for enhancing cellular uptake and optimizing antigens. DNA vaccines for various cancers and viral pathogens such as HIV, HPV, and hepatitis B and C are currently in development.

Some DNA vaccines are already in use. In 2005, a DNA vaccine against West Nile virus was approved for use in horses in the United States. Canada has also approved a DNA vaccine to protect fish from infectious hematopoietic necrosis virus.[4] A DNA vaccine against Japanese encephalitis virus was approved for use in humans in 2010 in Australia.[5]

## Clinical Focus

**Resolution**

Based on Olivia's symptoms, her physician made a preliminary diagnosis of bacterial meningitis without waiting for positive identification from the blood and CSF samples sent to the lab. Olivia was admitted to the hospital and treated with intravenous broad-spectrum antibiotics and rehydration therapy. Over the next several days, her condition began to improve, and new blood samples and lumbar puncture samples showed an absence of microbes in the blood and CSF with levels of white blood cells returning to normal. During this time, the lab produced a positive identification of Neisseria meningitidis, the causative agent of meningococcal meningitis, in her original CSF sample.

N. meningitidis produces a polysaccharide capsule that serves as a virulence factor. N. meningitidis tends to affect infants after they begin to lose the natural passive immunity provided by maternal antibodies. At one year of age, Olivia's maternal IgG antibodies would have disappeared, and she would not have developed memory cells capable of recognizing antigens associated with the polysaccharide capsule of the N. meningitidis. As a result, her adaptive immune system was unable to produce protective antibodies to combat the infection, and without antibiotics she may not have survived. Olivia's infection likely would have been avoided altogether had she been vaccinated. A conjugate vaccine to prevent meningococcal meningitis is available and approved for infants as young as two months of age. However, current vaccination schedules in the United States recommend that the vaccine be administered at age 11–12 with a booster at age 16.

*Go back to the previous Clinical Focus box.*

## Link to Learning

In countries with developed public health systems, many vaccines are routinely administered to children and adults. Vaccine schedules are changed periodically, based on new information and research results gathered by public health agencies. In the United States, the CDC publishes schedules and other updated information about vaccines.

# Key Concepts and Summary

- Adaptive immunity can be divided into four distinct classifications: **natural active immunity, natural passive immunity, artificial passive immunity,** and **artificial active immunity.**
- Artificial active immunity is the foundation for **vaccination** and vaccine development. Vaccination programs not only confer artificial immunity on individuals, but also foster **herd immunity** in populations.
- **Variolation** against smallpox originated in the 10th century in China, but the procedure was risky because it could cause the disease it was intended to prevent. Modern vaccination was developed by Edward Jenner, who developed the practice of inoculating patients with infectious materials from cowpox lesions to prevent smallpox.
- **Live attenuated vaccines** and **inactivated vaccines** contain whole pathogens that are weak, killed, or inactivated. **Subunit vaccines, toxoid vaccines,** and **conjugate vaccines** contain acellular components with antigens that stimulate an immune response.

## Footnotes

1. K. Mupapa, M. Massamba, K. Kibadi, K. Kivula, A. Bwaka, M. Kipasa, R. Colebunders, J. J. Muyembe-Tamfum. “Treatment of Ebola Hemorrhagic Fever with Blood Transfusions from Convalescent Patients.” *Journal of Infectious Diseases* 179 Suppl. (1999): S18–S23.
2. Elizabeth Yale. “Why Anti-Vaccination Movements Can Never Be Tamed.” *Religion & Politics*, July 22, 2014. http://religionandpolitics.org/2014/...never-be-tamed.
3. N. J. Willis. “Edward Jenner and the Eradication of Smallpox.” *Scottish Medical Journal* 42 (1997): 118–121.
4. M. Alonso and J. C. Leong. “Licensed DNA Vaccines Against Infectious Hematopoietic Necrosis Virus (IHNV).” *Recent Patents on DNA & Gene Sequences (Discontinued)* 7 no. 1 (2013): 62–65, issn 1872-2156/2212-3431. doi 10.2174/1872215611307010009.
5. S.B. Halstead and S. J. Thomas. “New Japanese Encephalitis Vaccines: Alternatives to Production in Mouse Brain.” *Expert Review of Vaccines* 10 no. 3 (2011): 355–64.

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# 5.6: Review Questions

## Multiple Choice

1. Antibodies are produced by _____.
   A. plasma cells
   B. T cells
   C. bone marrow
   D. B cells

*Answer available at the end of this section.*

2. Cellular adaptive immunity is carried out by _____.
   A. B cells
   B. T cells
   C. bone marrow
   D. neutrophils

*Answer available at the end of this section.*

3. A single antigen molecule may be composed of individual _____.
   A. T-cell receptors
   B. B-cell receptors
   C. MHC II
   D. epitopes

*Answer available at the end of this section.*

4. Which class of molecules is the most antigenic?
   A. polysaccharides
   B. lipids
   C. proteins
   D. carbohydrates

*Answer available at the end of this section.*

5. MHC I molecules present
   A. processed foreign antigens from phagolysosomes.
   B. processed self-antigens from proteasomes.
   C. antibodies.
   D. T cell antigens.

*Answer available at the end of this section.*

6. MHC II molecules present
   A. processed self-antigens from proteasomes.
   B. processed foreign antigens from phagolysosomes.
   C. antibodies.
   D. T cell receptors.

*Answer available at the end of this section.*

7. Which type of antigen-presenting molecule is found on all nucleated cells?
   A. MHC II
   B. MHC I

C. antibodies
D. B-cell receptors

*Answer available at the end of this section.*

8. Which type of antigen-presenting molecule is found only on macrophages, dendritic cells, and B cells?
   A. MHC I
   B. MHC II
   C. T-cell receptors
   D. B-cell receptors

*Answer available at the end of this section.*

9. What is a superantigen?
   A. a protein that is highly efficient at stimulating a single type of productive and specific T cell response
   B. a protein produced by antigen-presenting cells to enhance their presentation capabilities
   C. a protein produced by T cells as a way of increasing the antigen activation they receive from antigen-presenting cells
   D. a protein that activates T cells in a nonspecific and uncontrolled manner

*Answer available at the end of this section.*

10. To what does the TCR of a helper T cell bind?
    A. antigens presented with MHC I molecules
    B. antigens presented with MHC II molecules
    C. free antigen in a soluble form
    D. haptens only

*Answer available at the end of this section.*

11. Cytotoxic T cells will bind with their TCR to which of the following?
    A. antigens presented with MHC I molecules
    B. antigens presented with MHC II molecules
    C. free antigen in a soluble form
    D. haptens only

*Answer available at the end of this section.*

12. A _____ molecule is a glycoprotein used to identify and distinguish white blood cells.
    A. T-cell receptor
    B. B-cell receptor
    C. MHC I
    D. cluster of differentiation

*Answer available at the end of this section.*

13. Name the T helper cell subset involved in antibody production.
    A. $T_H1$
    B. $T_H2$
    C. $T_H17$
    D. CTL

*Answer available at the end of this section.*

14. Which of the following would be a T-dependent antigen?
    A. lipopolysaccharide
    B. glycolipid
    C. protein
    D. carbohydrate

*Answer available at the end of this section.*

15. Which of the following would be a BCR?
    A. CD4
    B. MHC II
    C. MHC I
    D. IgD

*Answer available at the end of this section.*

16. Which of the following does not occur during the lag period of the primary antibody response?
    A. activation of helper T cells
    B. class switching to IgG
    C. presentation of antigen with MHC II
    D. binding of antigen to BCRs

*Answer available at the end of this section.*

17. A patient is bitten by a dog with confirmed rabies infection. After treating the bite wound, the physician injects the patient with antibodies that are specific for the rabies virus to prevent the development of an active infection. This is an example of:
    A. Natural active immunity
    B. Artificial active immunity
    C. Natural passive immunity
    D. Artificial passive immunity

*Answer available at the end of this section.*

18. A patient gets a cold, and recovers a few days later. The patient's classmates come down with the same cold roughly a week later, but the original patient does not get the same cold again. This is an example of:
    A. Natural active immunity
    B. Artificial active immunity
    C. Natural passive immunity
    D. Artificial passive immunity

*Answer available at the end of this section.*

## Matching

19. Match the antibody class with its description.

| | |
|---|---|
| ___IgA | A. This class of antibody is the only one that can cross the placenta. |
| ___IgD | B. This class of antibody is the first to appear after activation of B cells. |
| ___IgE | C. This class of antibody is involved in the defense against parasitic infections and involved in allergic responses. |
| ___IgG | D. This class of antibody is found in very large amounts in mucus secretions. |
| ___IgM | E. This class of antibody is not secreted by B cells but is expressed on the surface of naïve B cells. |

*Answer available at the end of this section.*

20. Match each type of vaccine with the corresponding example.

| | |
|---|---|
| ___inactivated vaccine | A. Weakened influenza virions that can only replicate in the slightly lower temperatures of the nasal passages are sprayed into the nose. They do not cause serious flu symptoms, but still produce an active infection that induces a protective adaptive immune response. |

| | |
|---|---|
| ___live attenuated vaccine | B. Tetanus toxin molecules are harvested and chemically treated to render them harmless. They are then injected into a patient's arm. |
| ___toxoid vaccine | C. Influenza virus particles grown in chicken eggs are harvested and chemically treated to render them noninfectious. These immunogenic particles are then purified and packaged and administered as an injection. |
| ___subunit vaccine | D. The gene for hepatitis B virus surface antigen is inserted into a yeast genome. The modified yeast is grown and the virus protein is produced, harvested, purified, and used in a vaccine. |

*Answer available at the end of this section.*

## Fill in the Blank

21. There are two critically important aspects of adaptive immunity. The first is specificity, while the second is _____.

*Answer available at the end of this section.*

22. _____ immunity involves the production of antibody molecules that bind to specific antigens.

*Answer available at the end of this section.*

23. The heavy chains of an antibody molecule contain _____ region segments, which help to determine its class or isotype.

*Answer available at the end of this section.*

24. The variable regions of the heavy and light chains form the _____ sites of an antibody.

*Answer available at the end of this section.*

25. MHC molecules are used for antigen _____ to T cells.

*Answer available at the end of this section.*

26. MHC II molecules are made up of two subunits (α and β) of approximately equal size, whereas MHC I molecules consist of a larger α subunit and a smaller subunit called _____.

*Answer available at the end of this section.*

27. A _____ T cell will become activated by presentation of foreign antigen associated with an MHC I molecule.

*Answer available at the end of this section.*

28. A _____ T cell will become activated by presentation of foreign antigen in association with an MHC II molecule.

*Answer available at the end of this section.*

29. A TCR is a protein dimer embedded in the plasma membrane of a T cell. The _____ region of each of the two protein chains is what gives it the capability to bind to a presented antigen.

*Answer available at the end of this section.*

30. Peripheral tolerance mechanisms function on T cells after they mature and exit the _____.

*Answer available at the end of this section.*

31. Both _____ and effector T cells are produced during differentiation of activated T cells.

*Answer available at the end of this section.*

32. _____ antigens can stimulate B cells to become activated but require cytokine assistance delivered by helper T cells.

*Answer available at the end of this section.*

33. T-independent antigens can stimulate B cells to become activated and secrete antibodies without assistance from helper T cells. These antigens possess _____ antigenic epitopes that cross-link BCRs.

*Answer available at the end of this section.*

34. A(n) _____ pathogen is in a weakened state; it is still capable of stimulating an immune response but does not cause a disease.

*Answer available at the end of this section.*

35. _____ immunity occurs when antibodies from one individual are harvested and given to another to protect against disease or treat active disease.

*Answer available at the end of this section.*

36. In the practice of _____, scabs from smallpox victims were used to immunize susceptible individuals against smallpox.

*Answer available at the end of this section.*

## Short Answer

37. What is the difference between humoral and cellular adaptive immunity?

38. What is the difference between an antigen and a hapten?

39. Describe the mechanism of antibody-dependent cell-mediated cytotoxicity.

40. What is the basic difference in effector function between helper and cytotoxic T cells?

41. What necessary interactions are required for activation of helper T cells and activation/effector function ofcytotoxic T cells?

42. Briefly compare the pros and cons of inactivated versus live attenuated vaccines.

## Critical Thinking

43. Which mechanism of antigen presentation would be used to present antigens from a cell infected with a virus?

44. Which pathway of antigen presentation would be used to present antigens from an extracellular bacterial infection?

45. A patient lacks the ability to make functioning T cells because of a genetic disorder. Would this patient's B cells be able to produce antibodies in response to an infection? Explain your answer.

## Answers

**Multiple Choice**

A

**Multiple Choice**

B

**Multiple Choice**

D

**Multiple Choice**

C

**Multiple Choice**

A

**Multiple Choice**

B

**Multiple Choice**

B

**Multiple Choice**

B

**Multiple Choice**

D

**Multiple Choice**

B

**Multiple Choice**

A

**Multiple Choice**

D

**Multiple Choice**

B

**Multiple Choice**

C

**Multiple Choice**

D

**Multiple Choice**

B

**Multiple Choice**

D

**Multiple Choice**

A

**Matching**

D, E, C, A, B

**Matching**

C, A, B, D

**Fill in the Blank**

memory

**Fill in the Blank**

Humoral

**Fill in the Blank**

constant

**Fill in the Blank**

antigen-binding

**Fill in the Blank**

presentation

**Fill in the Blank**

$\beta_2$ microglobulin

**Fill in the Blank**

cytotoxic

**Fill in the Blank**

helper

**Fill in the Blank**

variable

**Fill in the Blank**

thymus

**Fill in the Blank**

memory

**Fill in the Blank**
T-dependent

**Fill in the Blank**
repetitive

**Fill in the Blank**
attenuated

**Fill in the Blank**
Artificial passive

**Fill in the Blank**
variolation

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# 6: Immune System, Part 1 (Video)

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# 7: Immune System, Part 2 (Video)

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# WEEK 5


## 9: Antimicrobial Drugs

9.1: History of Chemotherapy and Antimicrobial Discovery

9.2: Fundamentals of Antimicrobial Chemotherapy

9.3: Mechanisms of Antibacterial Drugs

9.4: Mechanisms of Other Antimicrobial Drugs

9.5: Drug Resistance

9.6: Testing the Effectiveness of Antimicrobials

9.7: Current Strategies for Antimicrobial Discovery

9.8: Review Questions

## 10: Antibiotics vs. Bacteria - Fighting the Resistance (Video)


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# 9: ANTIMICROBIAL DRUGS

In nature, some microbes produce substances that inhibit or kill other microbes that might otherwise compete for the same resources. Humans have successfully exploited these abilities, using microbes to mass-produce substances that can be used as antimicrobial drugs. Since their discovery, antimicrobial drugs have saved countless lives, and they remain an essential tool for treating and controlling infectious disease. But their widespread and often unnecessary use has had an unintended side effect: the rise of multidrug-resistant microbial strains. In this chapter, we will discuss how antimicrobial drugs work, why microbes develop resistance, and what health professionals can do to encourage responsible use of antimicrobials.




Figure 9.1: First mass produced in the 1940s, penicillin was instrumental in saving millions of lives during World War II and was considered a wonder drug.[1] Today, overprescription of antibiotics (especially for childhood illnesses) has contributed to the evolution of drug-resistant pathogens. (credit left: modification of work by Chemical Heritage Foundation; credit right: modification of work by U.S. Department of Defense)

## Chapter Outline

9.1: History of Chemotherapy and Antimicrobial Discovery

9.2: Fundamentals of Antimicrobial Chemotherapy

9.3: Mechanisms of Antibacterial Drugs

9.4: Mechanisms of Other Antimicrobial Drugs

9.5: Drug Resistance

9.6: Testing the Effectiveness of Antimicrobials

9.7: Current Strategies for Antimicrobial Discovery

9.8: Review Questions

## Footnotes

1. “Treatment of War Wounds: A Historical Review.” *Clinical Orthopaedics and Related Research* 467 no. 8 (2009):2168–2191.

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# 9.1: History of Chemotherapy and Antimicrobial Discovery

Learning Objectives

- Compare and contrast natural, semisynthetic, and synthetic antimicrobial drugs
- Describe the chemotherapeutic approaches of ancient societies
- Describe the historically important individuals and events that led to the development of antimicrobial drugs

Most people associate the term chemotherapy with treatments for cancer. However, chemotherapy is actually a broader term that refers to any use of chemicals or drugs to treat disease. Chemotherapy may involve drugs that target cancerous cells or tissues, or it may involve **antimicrobial drugs** that target infectious microorganisms. Antimicrobial drugs typically work by destroying or interfering with microbial structures and enzymes, either killing microbial cells or inhibiting of their growth. But before we examine how these drugs work, we will briefly explore the history of humans' use of antimicrobials for the purpose of chemotherapy.

## Use of Antimicrobials in Ancient Societies

Although the discovery of antimicrobials and their subsequent widespread use is commonly associated with modern medicine, there is evidence that humans have been exposed to antimicrobial compounds for millennia. Chemical analyses of the skeletal remains of people from Nubia[1] (now found in present-day Sudan) dating from between 350 and 550 AD have shown residue of the antimicrobial agent tetracycline in high enough quantities to suggest the purposeful fermentation of tetracycline-producing Streptomyces during the beer-making process. The resulting beer, which was thick and gruel-like, was used to treat a variety of ailments in both adults and children, including gum disease and wounds. The antimicrobial properties of certain plants may also have been recognized by various cultures around the world, including Indian and Chinese herbalists (***Figure*** 9.1.1) who have long used plants for a wide variety of medical purposes. Healers of many cultures understood the antimicrobial properties of fungi and their use

Clinical Focus

**Part 1**

Marisa, a 52-year-old woman, was suffering from severe abdominal pain, swollen lymph nodes, fatigue, and a fever. She had just returned home from visiting extended family in her native country of Cambodia. While abroad, she received medical care in neighboring Vietnam for a compressed spinal cord. She still had discomfort when leaving Cambodia, but the pain increased as her trip home continued and her husband drove her straight from the airport to the emergency room.

Her doctor considers whether Marisa could be suffering from appendicitis, a urinary tract infection (UTI), or pelvic inflammatory disease (PID). However, each of those conditions is typically preceded or accompanied by additional symptoms. He considers the treatment she received in Vietnam for her compressed spinal cord, but abdominal pain is not usually associated with spinal cord compression. He examines her health history further.

- What type of infection or other condition may be responsible?
- What type of lab tests might the doctor order?

*Jump to the next Clinical Focus box.*

of moldy bread or other mold-containing products to treat wounds has been well documented for centuries.[2] Today, while about 80% of the world's population still relies on plant-derived medicines,[3] scientists are now discovering the active compounds conferring the medicinal benefits contained in many of these traditionally used plants.



***Figure*** 9.1.1 *For millennia, Chinese herbalists have used many different species of plants for the treatment of a wide variety of human ailments.*

check your understanding

- Give examples of how antimicrobials were used in ancient societies.

## The First Antimicrobial Drugs

Societies relied on traditional medicine for thousands of years; however, the first half of the 20th century brought an era of strategic drug discovery. In the early 1900s, the German physician and scientist Paul Ehrlich (1854–1915) set out to discover or synthesize chemical compounds capable of killing infectious microbes without harming the patient. In 1909, after screening more than 600 arsenic-containing compounds, Ehrlich's assistant Sahachiro Hata (1873–1938) found one such "magic bullet." Compound 606 targeted the bacterium *Treponema pallidum*, the causative agent of syphilis. Compound 606 was found to successfully cure syphilis in rabbits and soon after was marketed under the name Salvarsan as a remedy for the disease in humans (***Figure*** 9.1.2). Ehrlich's innovative approach of systematically screening a wide variety of compounds remains a common strategy for the discovery of new antimicrobial agents even today.

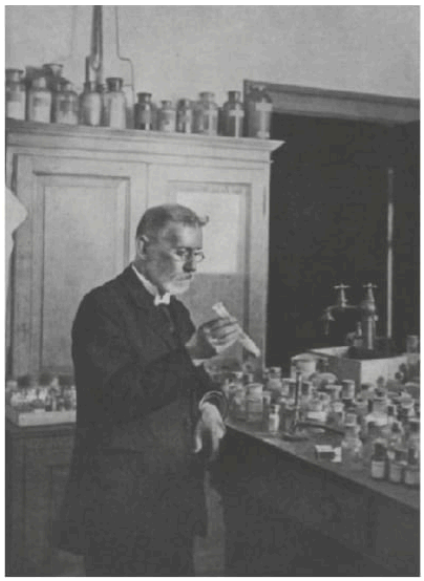


***Figure*** 9.1.2 *Paul Ehrlich was influential in the discovery of Compound 606, an antimicrobial agent that proved to be an effective treatment for syphilis.*

A few decades later, German scientists Josef Klarer, Fritz Mietzsch, and Gerhard Domagk discovered the antibacterial activity of a synthetic dye, prontosil, that could treat streptococcal and staphylococcal infections in mice. Domagk's own daughter was one of the first human recipients of the drug, which completely cured her of a severe streptococcal infection that had resulted from a poke with an embroidery needle. Gerhard Domagk (1895–1964) was awarded the Nobel Prize in Medicine in 1939 for his work with prontosil and sulfanilamide, the active breakdown product of prontosil in the body. Sulfanilamide, the first synthetic antimicrobial created, served as the foundation for the chemical development of a family of sulfa drugs. A **synthetic antimicrobial** is a drug that is developed from a chemical not found in nature. The success of the sulfa drugs led to the discovery and production of additional important classes of synthetic antimicrobials, including the quinolines and oxazolidinones.

A few years before the discovery of prontosil, scientist Alexander Fleming (1881–1955) made his own accidental discovery that turned out to be monumental. In 1928, Fleming returned from holiday and examined some old plates of staphylococci in his research laboratory at St. Mary's Hospital in London. He observed that contaminating mold growth (subsequently identified as a strain of Penicillium notatum) inhibited staphylococcal growth on one plate. Fleming, therefore, is credited with the discovery of **penicillin**, the first **natural antibiotic**, (***Figure*** 9.1.3). Further experimentation showed that penicillin from the mold was antibacterial against streptococci, meningococci, and *Corynebacterium diphtheriae*, the causative agent of diphtheria.

Fleming and his colleagues were credited with discovering and identifying penicillin, but its isolation and mass production were accomplished by a team of researchers at Oxford University under the direction of Howard Florey (1898–1968) and Ernst Chain (1906–1979) (***Figure*** 9.1.3). In 1940, the research team purified penicillin and reported its success as an antimicrobial agent against streptococcal infections in mice. Their subsequent work with human subjects also showed penicillin to be very effective. Because of their important work, Fleming, Florey, and Chain were awarded the Nobel Prize in Physiology and Medicine in 1945.

In the early 1940s, scientist Dorothy Hodgkin (1910–1994), who studied crystallography at Oxford University, used X-rays to analyze the structure of a variety of natural products. In 1946, she determined the structure of penicillin, for which she was awarded the Nobel Prize in Chemistry in 1964. Once the structure was understood, scientists could modify it to produce a variety of semisynthetic penicillins. A **semisynthetic antimicrobial** is a chemically modified derivative of a natural antibiotic. The chemical modifications are generally designed to increase the range of bacteria targeted, increase stability, decrease toxicity, or confer other properties beneficial for treating infections.

Penicillin is only one example of a natural antibiotic. Also in the 1940s, Selman Waksman (1888–1973) (***Figure*** 9.1.4), a prominent soil microbiologist at Rutgers University, led a research team that discovered several antimicrobials, including actinomycin, streptomycin, and neomycin. The discoveries of these antimicrobials stemmed from Waksman's study of fungi and the Actinobacteria, including soil bacteria in the genus *Streptomyces*, known for their natural production of a wide variety of antimicrobials. His work earned him the Nobel Prize in Physiology and Medicine in 1952. The actinomycetes are the source of more than half of all natural antibiotics[4] and continue to serve as an excellent reservoir for the discovery of novel antimicrobial agents. Some researchers argue that we have not yet come close to tapping the full antimicrobial potential of this group.[5]

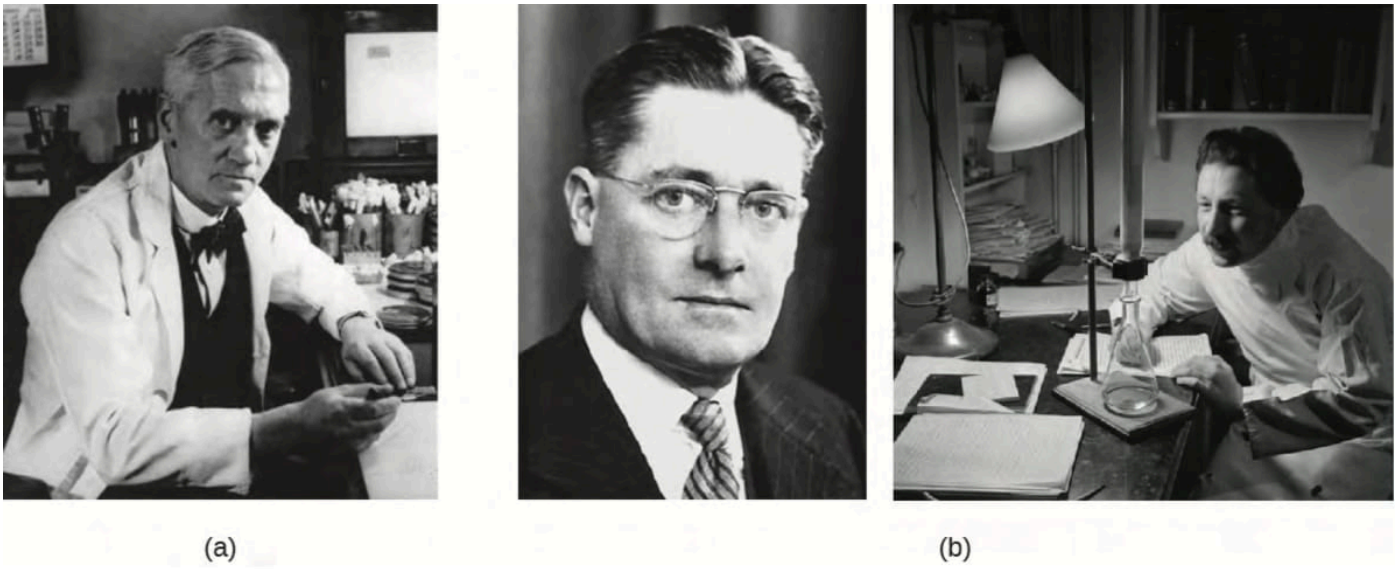



***Figure*** 9.1.3 *(a) Alexander Fleming was the first to discover a naturally produced antimicrobial, penicillin, in 1928. (b) Howard Florey and Ernst Chain discovered how to scale up penicillin production. Then they figured out how to purify it and showed its efficacy as an antimicrobial in animal and human trials in the early 1940s.*

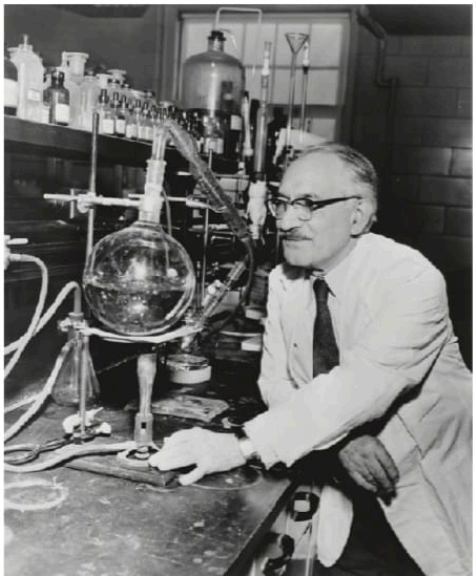


***Figure*** 9.1.4 *Selman Waksman was the first to show the vast antimicrobial production capabilities of a group of soil bacteria, the actinomycetes.*

check your understanding

- Why is the soil a reservoir for antimicrobial resistance genes?

## Summary

- **Antimicrobial drugs** produced by purposeful fermentation and/or contained in plants have been used as traditional medicines in many cultures for millennia.

- The purposeful and systematic search for a chemical “magic bullet” that specifically target infectious microbes was initiated by Paul Ehrlich in the early 20th century.
- The discovery of the **natural antibiotic**, penicillin, by Alexander Fleming in 1928 started the modern age of antimicrobial discovery and research.
- Sulfanilamide, the first **synthetic antimicrobial**, was discovered by Gerhard Domagk and colleagues and is a breakdown product of the synthetic dye, prontosil.

## References

1. M.L. Nelson et al. “Brief Communication: Mass Spectroscopic Characterization of Tetracycline in the Skeletal Remains of an Ancient Population from Sudanese Nubia 350–550 CE.” *American Journal of Physical Anthropology* 143 no. 1 (2010):151–154.

2. M. Wainwright. “Moulds in Ancient and More Recent Medicine.” *Mycologist* 3 no. 1 (1989):21–23.

3. S. Verma, S.P. Singh. “Current and Future Status of Herbal Medicines.” *Veterinary World* 1 no. 11 (2008):347–350.

4. J. Berdy. “Bioactive Microbial Metabolites.” *The Journal of Antibiotics* 58 no. 1 (2005):1–26.

5. M. Baltz. “Antimicrobials from Actinomycetes: Back to the Future.” *Microbe* 2 no. 3 (2007):125–131.

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# 9.2: Fundamentals of Antimicrobial Chemotherapy

Learning Objectives

- Contrast bacteriostatic versus bactericidal antibacterial activities
- Contrast broad-spectrum drugs versus narrow-spectrum drugs
- Explain the significance of superinfections
- Discuss the significance of dosage and the route of administration of a drug
- Identify factors and variables that can influence the side effects of a drug
- Describe the significance of positive and negative interactions between drugs

Several factors are important in choosing the most appropriate antimicrobial drug therapy, including bacteriostatic versus bactericidal mechanisms, spectrum of activity, dosage and route of administration, the potential for side effects, and the potential interactions between drugs. The following discussion will focus primarily on antibacterial drugs, but the concepts translate to other antimicrobial classes.

## Bacteriostatic Versus Bactericidal

Antibacterial drugs can be either **bacteriostatic** or bactericidal in their interactions with target bacteria. Bacteriostatic drugs cause a reversible inhibition of growth, with bacterial growth restarting after elimination of the drug. By contrast, **bactericidal** drugs kill their target bacteria. The decision of whether to use a bacteriostatic or bactericidal drugs depends on the type of infection and the immune status of the patient. In a patient with strong immune defenses, bacteriostatic and bactericidal drugs can be effective in achieving clinical cure. However, when a patient is immunocompromised, a bactericidal drug is essential for the successful treatment of infections. Regardless of the immune status of the patient, life-threatening infections such as acute endocarditis require the use of a bactericidal drug.

## Spectrum of Activity

The spectrum of activity of an antibacterial drug relates to diversity of targeted bacteria. A **narrow-spectrum antimicrobial** targets only specific subsets of bacterial pathogens. For example, some narrow-spectrum drugs only target gram-positive bacteria, whereas others target only gram-negative bacteria. If the pathogen causing an infection has been identified, it is best to use a narrow-spectrum antimicrobial and minimize collateral damage to the normal microbiota. A **broad-spectrum antimicrobial** targets a wide variety of bacterial pathogens, including both gram- positive and gram-negative species, and is frequently used as empiric therapy to cover a wide range of potential pathogens while waiting on the laboratory identification of the infecting pathogen. Broad-spectrum antimicrobials are also used for polymicrobic infections (mixed infection with multiple bacterial species), or as prophylactic prevention of infections with surgery/invasive procedures. Finally, broad-spectrum antimicrobials may be selected to treat an infection when a narrow-spectrum drug fails because of development of drug resistance by the target pathogen.

The risk associated with using broad-spectrum antimicrobials is that they will also target a broad spectrum of the normal microbiota, increasing the risk of a **superinfection**, a secondary infection in a patient having a preexisting infection. A superinfection develops when the antibacterial intended for the preexisting infection kills the protective microbiota, allowing another pathogen resistant to the antibacterial to proliferate and cause a secondary infection (***Figure*** 9.2.1). Common examples of superinfections that develop as a result of antimicrobial usage include yeast infections (candidiasis) and pseudomembranous colitis caused by *Clostridium difficile*, which can be fatal.

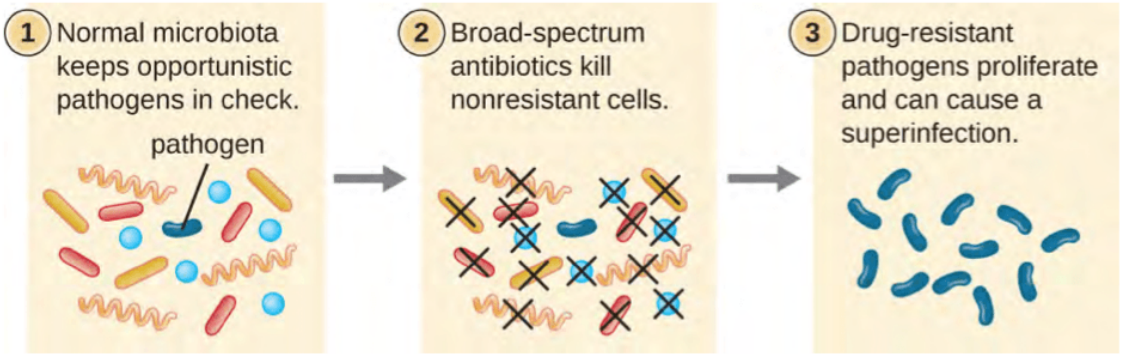



***Figure*** 9.2.1 *Broad-spectrum antimicrobial use may lead to the development of a superinfection. (credit: modification of work by Centers for Disease Control and Prevention)*

check your understanding

- What is a superinfection and how does one arise?

## Dosage and Route of Administration

The amount of medication given during a certain time interval is the **dosage**, and it must be determined carefully to ensure that optimum therapeutic drug levels are achieved at the site of infection without causing significant toxicity (side effects) to the patient. Each drug class is associated with a variety of potential side effects, and some of these are described for specific drugs later in this chapter. Despite best efforts to optimize dosing, allergic reactions and other potentially serious side effects do occur. Therefore, the goal is to select the optimum dosage that will minimize the risk of side effects while still achieving clinical cure, and there are important factors to consider when selecting the best dose and dosage interval. For example, in children, dose is based upon the patient's mass. However, the same is not true for adults and children 12 years of age and older, for which there is typically a single standard dose regardless of the patient's mass. With the great variability in adult body mass, some experts have argued that mass should be considered for all patients when determining appropriate dosage.[1] An additional consideration is how drugs are metabolized and eliminated from the body. In general, patients with a history of liver or kidney dysfunction may experience reduced drug metabolism or clearance from the body, resulting in increased drug levels that may lead to toxicity and make them more prone to side effects.

There are also some factors specific to the drugs themselves that influence appropriate dose and time interval between doses. For example, the half-life, or rate at which 50% of a drug is eliminated from the plasma, can vary significantly between drugs. Some drugs have a short half-life of only 1 hour and must be given multiple times a day, whereas other drugs have half-lives exceeding 12 hours and can be given as a single dose every 24 hours. Although a longer half-life can be considered an advantage for an antibacterial when it comes to convenient dosing intervals, the longer half-life can also be a concern for a drug that has serious side effects because drug levels may remain toxic for a longer time. Last, some drugs are dose dependent, meaning they are more effective when administered in large doses to provide high levels for a short time at the site of infection. Others are time dependent, meaning they are more effective when lower optimum levels are maintained over a longer period of time.

The **route of administration**, the method used to introduce a drug into the body, is also an important consideration for drug therapy. Drugs that can be administered orally are generally preferred because patients can more conveniently take these drugs at home. However, some drugs are not absorbed easily from the gastrointestinal (GI) tract into the bloodstream. These drugs are often useful for treating diseases of the intestinal tract, such as tapeworms treated with niclosamide, or for decontaminating the bowel, as with colistin. Some drugs that are not absorbed easily, such as bacitracin, polymyxin, and several antifungals, are available as topical preparations for treatment of superficial skin infections. Sometimes, patients may not initially be able to take oral medications because of their illness (e.g., vomiting, intubation for respirator). When this occurs, and when a chosen drug is not absorbed in the GI tract, administration of the drug by a parenteral route (intravenous or intramuscular injection) is preferred and typically is performed in health-care settings. For most drugs, the plasma levels achieved by intravenous administration is substantially higher than levels achieved by oral or intramuscular administration, and this can also be an important consideration when choosing the route of administration for treating an infection (***Figure*** 9.2.2).

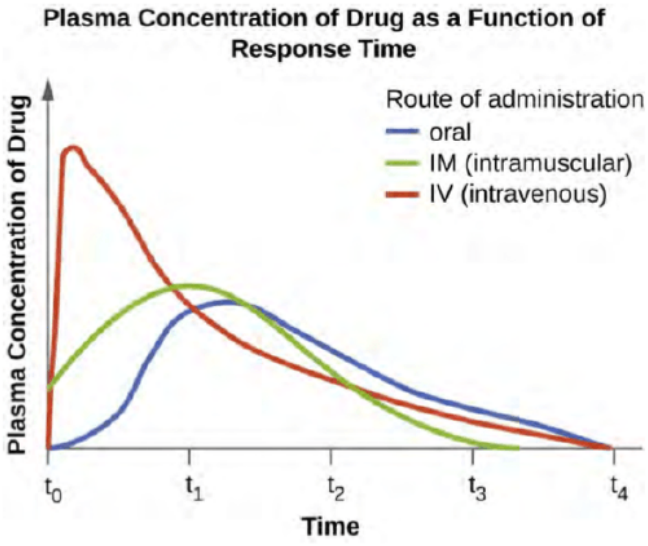



***Figure*** 9.2.2 *On this graph, t0 represents the time at which a drug dose is administered. The curves illustrate how plasma concentration of the drug changes over specific intervals of time ($t_1$ through $t_4$). As the graph shows, when a drug is administered intravenously, the concentration peaks very quickly and then gradually decreases. When drugs are administered orally or intramuscularly, it takes longer for the concentration to reach its peak.*

check your understanding

- List five factors to consider when determining the dosage of a drug.
- Name some typical side effects associated with drugs and identify some factors that might contribute to these side effects.

## Drug Interactions

For the optimum treatment of some infections, two antibacterial drugs may be administered together to provide a synergistic interaction that is better than the efficacy of either drug alone. A classic example of synergistic combinations is trimethoprim and sulfamethoxazole (Bactrim). Individually, these two drugs provide only bacteriostatic inhibition of bacterial growth, but combined, the drugs are bactericidal.

Whereas synergistic drug interactions provide a benefit to the patient, antagonistic interactions produce harmful effects. Antagonism can occur between two antimicrobials or between antimicrobials and nonantimicrobials being used to treat other conditions. The effects vary depending on the drugs involved, but antagonistic interactions may cause loss of drug activity, decreased therapeutic levels due to increased metabolism and elimination, or increased potential for toxicity due to decreased metabolism and elimination. As an example, some antibacterials are absorbed most effectively from the acidic environment of the stomach. If a patient takes antacids, however, this increases the pH of the stomach and negatively impacts the absorption of these antimicrobials, decreasing their effectiveness in treating an infection. Studies have also shown an association between use of some antimicrobials and failure of oral contraceptives.[2]

check your understanding

- Explain the difference between synergistic and antagonistic drug interactions.

Eye on Ethics

**Resistance Police**

In the United States and many other countries, most antimicrobial drugs are self-administered by patients at home. Unfortunately, many patients stop taking antimicrobials once their symptoms dissipate and they feel better. If a 10-day course of treatment is prescribed, many patients only take the drug for 5 or 6 days, unaware of the negative consequences of not completing the full course of treatment. A shorter course of treatment not only fails to kill the target organisms to expected levels, it also selects for drug-resistant variants within the target population and within the patient's microbiota.

Patients' nonadherence especially amplifies drug resistance when the recommended course of treatment is long. Treatment for tuberculosis (TB) is a case in point, with the recommended treatment lasting from 6 months to a year. The CDC estimates that about one-third of the world's population is infected with TB, most living in underdeveloped or underserved regions where antimicrobial drugs are available over the counter. In such countries, there may be even lower rates of adherence than in developed areas. Nonadherence leads to antibiotic resistance and more difficulty in controlling pathogens. As a direct result, the emergence of multidrug- resistant and extensively drug-resistant strains of TB is becoming a huge problem.

Overprescription of antimicrobials also contributes to antibiotic resistance. Patients often demand antibiotics for diseases that do not require them, like viral colds and ear infections. Pharmaceutical companies aggressively market drugs to physicians and clinics, making it easy for them to give free samples to patients, and some pharmacies even offer certain antibiotics free to low-income patients with a prescription.

In recent years, various initiatives have aimed to educate parents and clinicians about the judicious use of antibiotics. However, a recent study showed that, between 2000 and 2013, the parental expectation for antimicrobial prescriptions for children actually increased (***Figure*** 9.2.3).

One possible solution is a regimen called directly observed therapy (DOT), which involves the supervised administration of medications to patients. Patients are either required to visit a health-care facility to receive their medications, or health-care providers must administer medication in patients' homes or another designated location. DOT has been implemented in many cases for the treatment of TB and has been shown to be effective; indeed, DOT is an integral part of WHO's global strategy for eradicating TB.[3],[4] But is this a practical strategy for all antibiotics? Would patients taking penicillin, for example, be more or less likely to adhere to the full course of treatment if they had to travel to a health-care facility for each dose? And who would pay for the increased cost associated with DOT? When it comes to overprescription, should someone be policing physicians or drug companies to enforce best practices? What group should assume this responsibility, and what penalties would be effective in discouraging overprescription?

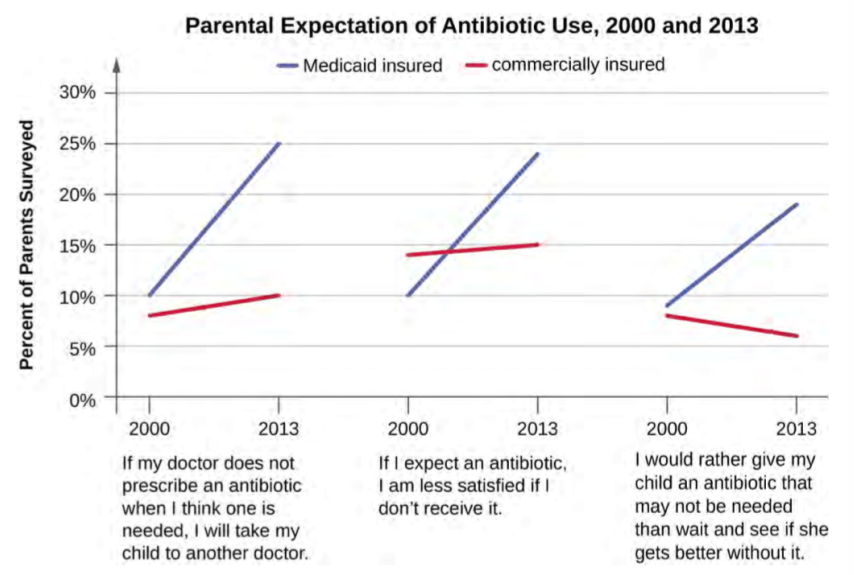



***Figure*** 9.2.3 *This graph indicates trends in parental expectations related to prescription of antibiotics based on a recent study.*[5] *Among parents of Medicaid-insured children, there was a clear upward trend in parental expectations for prescription antibiotics. Expectations were relatively stable (and lesser) among parents whose children were commercially insured, suggesting that these parents were somewhat better informed than those with Medicaid-insured children.*

## Summary

- Antimicrobial drugs can be **bacteriostatic** or **bactericidal**, and these characteristics are important considerations when selecting the most appropriate drug.
- The use of **narrow-spectrum** antimicrobial drugs is preferred in many cases to avoid **superinfection** and the development of antimicrobial resistance.
- **Broad-spectrum** antimicrobial use is warranted for serious systemic infections when there is no time to determine the causative agent, when narrow-spectrum antimicrobials fail, or for the treatment or prevention of infections with multiple types of microbes.
- The **dosage** and **route of administration** are important considerations when selecting an antimicrobial to treat and infection. Other considerations include the patient's age, mass, ability to take oral medications, liver and kidney function, and possible interactions with other drugs the patient may be taking.

## References

1. M.E. Falagas, D.E. Karageorgopoulos. "Adjustment of Dosing of Antimicrobial Agents for Bodyweight in Adults." *The Lancet* 375 no. 9710 (2010):248–251.

2. B.D. Dickinson et al. "Drug Interactions between Oral Contraceptives and Antibiotics." *Obstetrics & Gynecology* 98, no. 5 (2001):853–860.

3. Centers for Disease Control and Prevention. "Tuberculosis (TB)." http://www.cdc.gov/tb/education/ssmo...s9reading2.htm. Accessed June 2, 2016.

4. World Health Organization. "Tuberculosis (TB): The Five Elements of DOTS." http://www.who.int/tb/dots/whatisdots/en/. Accessed June 2, 2016.

5. Vaz, L.E., et al. "Prevalence of Parental Misconceptions About Antibiotic Use." *Pediatrics* 136 no.2 (August 2015). DOI: 10.1542/

peds.2015-0883.

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# 9.3: Mechanisms of Antibacterial Drugs

Learning Objective

- Describe the mechanisms of action associated with drugs that inhibit cell wall biosynthesis, protein synthesis, membrane function, nucleic acid synthesis, and metabolic pathways

An important quality for an antimicrobial drug is selective toxicity, meaning that it selectively kills or inhibits the growth of microbial targets while causing minimal or no harm to the host. Most antimicrobial drugs currently in clinical use are antibacterial because the prokaryotic cell provides a greater variety of unique targets for selective toxicity, in comparison to fungi, parasites, and viruses. Each class of antibacterial drugs has a unique mode of action(the way in which a drug affects microbes at the cellular level), and these are summarized in ***Figure*** 9.3.1 and ***Table*** 9.3.1.

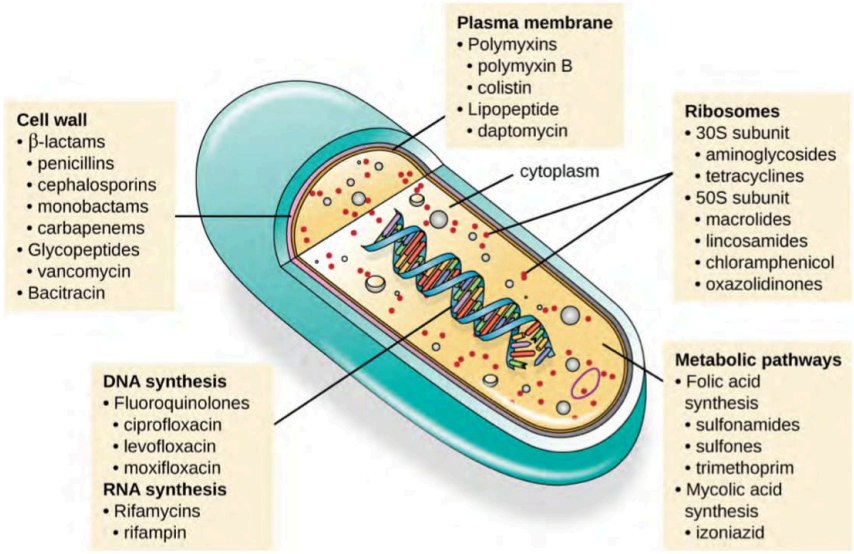



***Figure*** 9.3.1 *There are several classes of antibacterial compounds that are typically classified based on their bacterial target.*

**Common Antibacterial Drugs by Mode of Action**

| Mode of Action | Target | Drug Class |
|---|---|---|
| Inhibit cell wall biosynthesis | Penicillin-binding proteins | β-lactams: penicillins, cephalosporins, monobactams, carbapenems |
| | Peptidoglycan subunits | Glycopeptides |
| | Peptidoglycan subunit transport | Bacitracin |
| Inhibit biosynthesis of proteins | 30S ribosomal subunit | Aminoglycosides, tetracyclines |
| | 50S ribosomal subunit | Macrolides, lincosamides, chloramphenicol, oxazolidinones |
| Disrupt membranes | Lipopolysaccharide, inner and outer membranes | Polymyxin B, colistin, daptomycin |
| Inhibit nucleic acid synthesis | RNA | Rifamycin |
| | DNA | Fluoroquinolones |
| Antimetabolites | Folic acid synthesis enzyme | Sulfonamides, trimethoprim |
| | Mycolic acid synthesis enzyme | Isonicotinic acid hydrazide |
| Mycobacterial adenosine triphosphate (ATP) synthase inhibitor | Mycobacterial ATP synthase | Diarylquinoline |

***Table*** 9.3.1

# Inhibitors of Cell Wall Biosynthesis

Several different classes of antibacterials block steps in the biosynthesis of peptidoglycan, making cells more susceptible to osmotic lysis (***Table*** 9.3.2). Therefore, antibacterials that target cell wall biosynthesis are bactericidal in their action. Because human cells do not make peptidoglycan, this mode of action is an excellent example of selective toxicity.

Penicillin, the first antibiotic discovered, is one of several antibacterials within a class called **β-lactams**. This group of compounds includes the penicillins, cephalosporins, monobactams, and carbapenems, and is characterized by the presence of a β-lactam ring found within the central structure of the drug molecule (***Figure*** 9.3.2). The β- lactam antibacterials block the crosslinking of peptide chains during the biosynthesis of new peptidoglycan in the bacterial cell wall. They are able to block this process because the β-lactam structure is similar to the structure of the peptidoglycan subunit component that is recognized by the crosslinking transpeptidase enzyme, also known as a penicillin-binding protein (PBP). Although the β-lactam ring must remain unchanged for these drugs to retain their antibacterial activity, strategic chemical changes to the R groups have allowed for development of a wide variety of semisynthetic β-lactam drugs with increased potency, expanded spectrum of activity, and longer half-lives for better dosing, among other characteristics.

Penicillin G and penicillin V are natural antibiotics from fungi and are primarily active against gram-positive bacterial pathogens, and a few gram-negative bacterial pathogens such as Pasteurella multocida. ***Figure*** 9.3.2 summarizes the semisynthetic development of some of the penicillins. Adding an amino group (-NH2) to penicillin G created the aminopenicillins (i.e., ampicillin and amoxicillin) that have increased spectrum of activity against more gram- negative pathogens. Furthermore, the addition of a hydroxyl group (-OH) to amoxicillin increased acid stability, which allows for improved oral absorption. Methicillin is a semisynthetic penicillin that was developed to address the spread of enzymes (penicillinases) that were inactivating the other penicillins. Changing the R group of penicillin G to the more bulky dimethoxyphenyl group provided protection of the β-lactam ring from enzymatic destruction by penicillinases, giving us the first penicillinase-resistant penicillin.

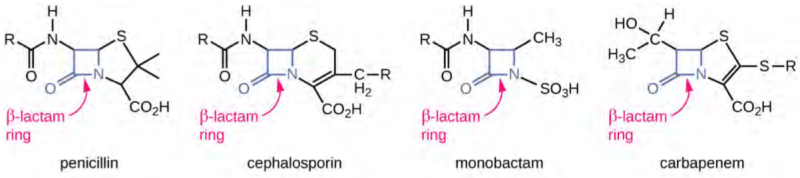
Similar to the penicillins, **cephalosporins** contain a β-lactam ring (***Figure*** 9.3.2) and block the transpeptidase activity of penicillin-binding proteins. However, the β-lactam ring of cephalosporins is fused to a six-member ring, rather than the five-member ring found in penicillins. This chemical difference provides cephalosporins with an increased resistance to enzymatic inactivation by **β-lactamases**. The drug cephalosporin C was originally isolated from the fungus Cephalosporium acremonium in the 1950s and has a similar spectrum of activity to that of penicillin against gram-positive bacteria but is active against more gram-negative bacteria than penicillin. Another important structural difference is that cephalosporin C possesses two R groups, compared with just one R group for penicillin, and this provides for greater diversity in chemical alterations and development of semisynthetic cephalosporins. The family of semisynthetic cephalosporins is much larger than the penicillins, and these drugs have been classified into generations based primarily on their spectrum of activity, increasing in spectrum from the narrow-spectrum, first-generation cephalosporins to the broad-spectrum, fourth-generation cephalosporins. A new fifth-generation cephalosporin has been developed that is active against methicillin-resistant Staphylococcus aureus (MRSA).

The carbapenems and monobactams also have a β-lactam ring as part of their core structure, and they inhibit the transpeptidase activity of penicillin-binding proteins. The only monobactam used clinically is aztreonam. It is a narrow-spectrum antibacterial with activity only against gram-negative bacteria. In contrast, the carbapenem family includes a variety of semisynthetic drugs (imipenem, meropenem, and doripenem) that provide very broad-spectrum activity against gram-positive and gram-negative bacterial pathogens.

The drug **vancomycin**, a member of a class of compounds called the **glycopeptides**, was discovered in the 1950s as a natural antibiotic from the actinomycete Amycolatopsis orientalis. Similar to the β-lactams, vancomycin inhibits cell wall biosynthesis and is bactericidal. However, in contrast to the β-lactams, the structure of vancomycin is not similar to that of cell-wall peptidoglycan subunits and does not directly inactivate penicillin-binding proteins. Rather, vancomycin is a very large, complex molecule that binds to the end of the peptide chain of cell wall precursors, creating a structural blockage that prevents the cell wall subunits from being incorporated into the growing N-acetylglucosamine and N-acetylmuramic acid (NAM-NAG) backbone of the peptidoglycan structure (transglycosylation). Vancomycin also structurally blocks transpeptidation. Vancomycin is bactericidal against gram-positive bacterial pathogens, but it is not active against gram-negative bacteria because of its inability to penetrate the protective outer membrane.

The drug **bacitracin** consists of a group of structurally similar peptide antibiotics originally isolated from Bacillus subtilis. Bacitracin blocks the activity of a specific cell-membrane molecule that is responsible for the movement of peptidoglycan precursors from the cytoplasm to the exterior of the cell, ultimately preventing their incorporation into the cell wall. Bacitracin

is effective against a wide range of bacteria, including gram-positive organisms found on the skin, such as Staphylococcus and Streptococcus. Although it may be administered orally or intramuscularly in some circumstances, bacitracin has been shown to be nephrotoxic (damaging to the kidneys). Therefore, it is more commonly combined with neomycin and polymyxin in topical ointments such as Neosporin.




| R group | $-CH_2-C_6H_5$ | $CH_2-O-C_6H_5$ | $-CH(NH_2)-C_6H_5$ | $-CH(NH_2)-C_6H_4-OH$ | $C_6H_3(CH_3O)_2$ |
|---|---|---|---|---|---|
| **Drug name** | penicillin G | penicillin V | ampicillin | amoxicillin | methicillin |
| **Spectrum of activity** | G+ and a few G− | similar to penicillin G | G+ and more G− than penicillin | similar to ampicillin | G+ only, including β-lactamase producers |
| **Route of administration** | parenteral | oral | parenteral and oral | oral (better than ampicillin) | parenteral |

***Figure*** 9.3.2 *Penicillins, cephalosporins, monobactams, and carbapenems all contain a β-lactam ring, the site of attack by inactivating β-lactamase enzymes. Although they all share the same nucleus, various penicillins differ from each other in the structure of their R groups. Chemical changes to the R groups provided increased spectrum of activity, acid stability, and resistance to β-lactamase degradation.*

**Drugs that Inhibit Bacterial Cell Wall Synthesis**

| Mechanism of Action | Drug Class | Specific Drugs | Natural or Semisynthetic | Spectrum of Activity |
|---|---|---|---|---|
| Interact directly with PBPs and inhibit transpeptidase activity | Penicillins | Penicillin G, penicillin V | Natural | Narrow-spectrum against gram-positive and a few gram-negative bacteria |

| Mechanism of Action | Drug Class | Specific Drugs | Natural or Semisynthetic | Spectrum of Activity |
|---|---|---|---|---|
| | | Ampicillin, amoxicillin | Semisynthetic | Narrow-spectrum against gram-positive bacteria but with increased gram-negative spectrum |
| | | Methicillin | Semisynthetic | Narrow-spectrum against gram-positive bacteria only, including strains producing penicillinase |
| | Cephalosporins | Cephalosporin C | Natural | Narrow-spectrum similar to penicillin but with increased gram-negative spectrum |
| | | First-generation cephalosporins | Semisynthetic | Narrow-spectrum similar to cephalosporin C |
| | | Second-generation cephalosporins | Semisynthetic | Narrow-spectrum but with increased gram-negative spectrum compared with first generation |
| | | Third- and fourth-generation cephalosporins | Semisynthetic | Broad-spectrum against gram-positive and gram-negative bacteria, including some β-lactamase producers |
| | | Fifth-generation cephalosporins | Semisynthetic | Broad-spectrum against gram-positive and gram-negative bacteria, including MRSA |
| | Monobactams | Aztreonam | Semisynthetic | Narrow-spectrum against gram-negative bacteria, including some β-lactamase producers |
| | Carbapenems | Imipenem, meropenem, doripenem | Semisynthetic | Broadest spectrum of the β-lactams against gram-positive and gram-negative bacteria, including many β-lactamase producers |
| Large molecules that bind to the peptide chain of peptidoglycan subunits, blocking transglycosylation and transpeptidation | Glycopeptides | Vancomycin | Natural | Narrow spectrum against gram-positive bacteria only, including multidrug-resistant strains |

***Table*** 9.3.2

check your understanding

- Describe the mode of action of β-lactams.

## Inhibitors of Protein Biosynthesis

The cytoplasmic ribosomes found in animal cells (80S) are structurally distinct from those found in bacterial cells (70S), making protein biosynthesis a good selective target for antibacterial drugs. Several types of protein biosynthesis inhibitors are discussed in this section and are summarized in ***Figure*** 9.3.3.

## Protein Synthesis Inhibitors That Bind the 30S Subunit

Aminoglycosides are large, highly polar antibacterial drugs that bind to the 30S subunit of bacterial ribosomes, impairing the proofreading ability of the ribosomal complex. This impairment causes mismatches between codons and anticodons, resulting in the production of proteins with incorrect amino acids and shortened proteins that insert into the cytoplasmic membrane. Disruption of the cytoplasmic membrane by the faulty proteins kills the bacterial cells. The **aminoglycosides**, which include drugs such as streptomycin, gentamicin, neomycin, and kanamycin, are potent broad-spectrum antibacterials. However, aminoglycosides have been shown to be nephrotoxic (damaging to kidney), neurotoxic (damaging to the nervous system), and ototoxic (damaging to the ear).

Another class of antibacterial compounds that bind to the 30S subunit is the **tetracyclines**. In contrast to aminoglycosides, these drugs are bacteriostatic and inhibit protein synthesis by blocking the association of tRNAs with the ribosome during translation. Naturally occurring tetracyclines produced by various strains of *Streptomyces* were first discovered in the 1940s, and several semisynthetic tetracyclines, including doxycycline and tigecycline have also been produced. Although the tetracyclines are broad spectrum in their coverage of bacterial pathogens, side effects that can limit their use include phototoxicity, permanent discoloration of developing teeth, and liver toxicity with high doses or in patients with kidney impairment.

## Protein Synthesis Inhibitors That Bind the 50S Subunit

There are several classes of antibacterial drugs that work through binding to the 50S subunit of bacterial ribosomes. The macrolide antibacterial drugs have a large, complex ring structure and are part of a larger class of naturally produced secondary metabolites called polyketides, complex compounds produced in a stepwise fashion through the repeated addition of two-carbon

units by a mechanism similar to that used for fatty acid synthesis. Macrolides are broad-spectrum, bacteriostatic drugs that block elongation of proteins by inhibiting peptide bond formation between specific combinations of amino acids. The first macrolide was **erythromycin**. It was isolated in 1952 from *Streptomyces erythreus* and prevents translocation. Semisynthetic macrolides include azithromycin and telithromycin. Compared with erythromycin, **azithromycin** has a broader spectrum of activity, fewer side effects, and a significantly longer half-life (1.5 hours for erythromycin versus 68 hours for azithromycin) that allows for once-daily dosing and a short 3-day course of therapy (i.e., Zpac formulation) for most infections. Telithromycin is the first semisynthetic within the class known as ketolides. Although telithromycin shows increased potency and activity against macrolide- resistant pathogens, the US Food and Drug Administration (FDA) has limited its use to treatment of community- acquired pneumonia and requires the strongest “black box warning” label for the drug because of serious hepatotoxicity.

The **lincosamides** include the naturally produced **lincomycin** and semisynthetic **clindamycin**. Although structurally distinct from macrolides, lincosamides are similar in their mode of action to the macrolides through binding to the 50S ribosomal subunit and preventing peptide bond formation. Lincosamides are particularly active against streptococcal and staphylococcal infections.

The drug **chloramphenicol** represents yet another structurally distinct class of antibacterials that also bind to the 50S ribosome, inhibiting peptide bond formation. Chloramphenicol, produced by Streptomyces venezuelae, was discovered in 1947; in 1949, it became the first broad-spectrum antibiotic that was approved by the FDA. Although it is a natural antibiotic, it is also easily synthesized and was the first antibacterial drug synthetically mass produced. As a result of its mass production, broad-spectrum coverage, and ability to penetrate into tissues efficiently, chloramphenicol was historically used to treat a wide range of infections, from meningitis to typhoid fever to conjunctivitis. Unfortunately, serious side effects, such as lethal gray baby syndrome, and suppression of bone marrow production, have limited its clinical role. Chloramphenicol also causes anemia in two different ways. One mechanism involves the targeting of mitochondrial ribosomes within hematopoietic stem cells, causing a reversible, dose-dependent suppression of blood cell production. Once chloramphenicol dosing is discontinued, blood cell production returns to normal. This mechanism highlights the similarity between 70S ribosomes of bacteria and the 70S ribosomes within our mitochondria. The second mechanism of anemia is idiosyncratic (i.e., the mechanism is not understood), and involves an irreversible lethal loss of blood cell production known as aplastic anemia. This mechanism of aplastic anemia is not dose dependent and can develop after therapy has stopped. Because of toxicity concerns, chloramphenicol usage in humans is now rare in the United States and is limited to severe infections unable to be treated by less toxic antibiotics. Because its side effects are much less severe in animals, it is used in veterinary medicine.

The **oxazolidinones**, including linezolid, are a new broad-spectrum class of synthetic protein synthesis inhibitors that bind to the 50S ribosomal subunit of both gram-positive and gram-negative bacteria. However, their mechanism of action seems somewhat different from that of the other 50S subunit-binding protein synthesis inhibitors already discussed. Instead, they seem to interfere with formation of the initiation complex (association of the 50S subunit, 30S subunit, and other factors) for translation, and they prevent translocation of the growing protein from the ribosomal A site to the P site. ***Table*** 9.3.3 summarizes the protein synthesis inhibitors.

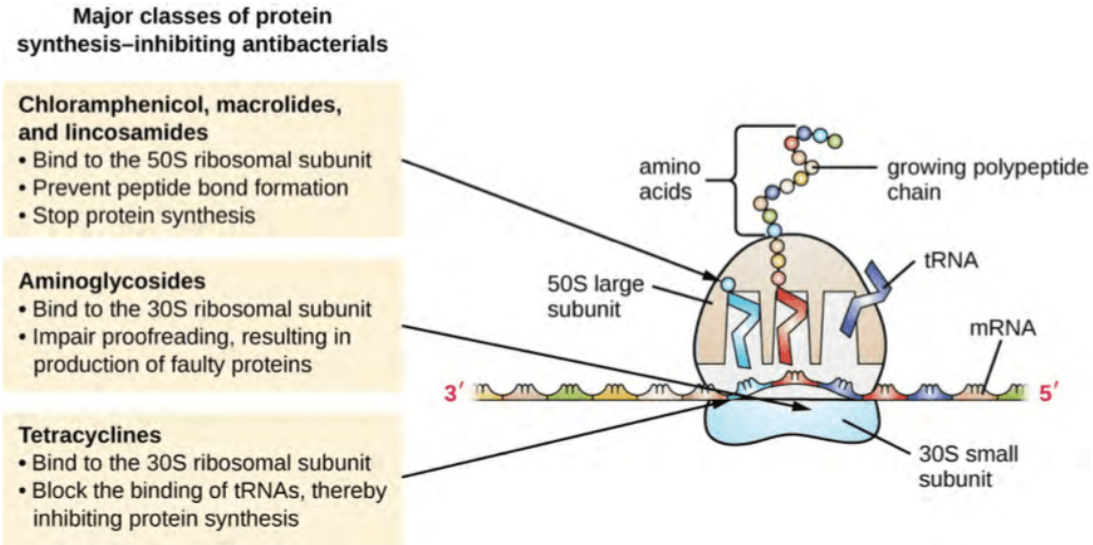



***Figure*** 9.3.3 *The major classes of protein synthesis inhibitors target the 30S or 50S subunits of cytoplasmic ribosomes.*

Drugs That Inhibit Bacterial Protein Synthesis

| Molecular Target | Mechanism of Action | Drug Class | Specific Drugs | Bacteriostatic or Bactericidal | Spectrum of Activity |
|---|---|---|---|---|---|
| 30S subunit | Causes mismatches between codons and anticodons, leading to faulty proteins that insert into and disrupt cytoplasmic membrane | Aminoglycosides | Streptomycin, gentamicin, neomycin, kanamycin | Bactericidal | Broad spectrum |
| | Blocks association of tRNAs with ribosome | Tetracyclines | Tetracycline, doxycycline, tigecycline | Bacteriostatic | Broad spectrum |
| 50S subunit | Blocks peptide bond formation between amino acids | Macrolides | Erythromycin, azithromycin, telithromycin | Bacteriostatic | Broad spectrum |
| | | Lincosamides | Lincomycin, clindamycin | Bacteriostatic | Narrow spectrum |
| | | Not applicable | Chloramphenicol | Bacteriostatic | Broad spectrum |
| | Interferes with the formation of the initiation complex between 50S and 30S subunits and other factors. | Oxazolidinones | Linezolid | Bacteriostatic | Broad spectrum |

***Table*** 9.3.3

check your understanding

- Compare and contrast the different types of protein synthesis inhibitors.

# Inhibitors of Membrane Function

A small group of antibacterials target the bacterial membrane as their mode of action (***Table*** 9.3.4). The **polymyxins** are natural polypeptide antibiotics that were first discovered in 1947 as products of *Bacillus polymyxa*; only polymyxin B and polymyxin E (**colistin**) have been used clinically. They are lipophilic with detergent-like properties and interact with the lipopolysaccharide component of the outer membrane of gram-negative bacteria, ultimately disrupting both their outer and inner membranes and killing the bacterial cells. Unfortunately, the membrane-targeting mechanism is not a selective toxicity, and these drugs also target and damage the membrane of cells in the kidney and nervous system when administered systemically. Because of these serious side effects and their poor absorption from the digestive tract, polymyxin B is used in over-the-counter topical antibiotic ointments (e.g., Neosporin), and oral colistin was historically used only for bowel decontamination to prevent infections originating from bowel microbes in immunocompromised patients or for those undergoing certain abdominal surgeries. However, the emergence and spread of multidrug-resistant pathogens has led to increased use of intravenous colistin in hospitals, often as a drug of last resort to treat serious infections. The antibacterial **daptomycin** is a cyclic lipopeptide produced by *Streptomyces roseosporus* that seems to work like the polymyxins, inserting in the bacterial cell membrane and disrupting it. However, in contrast to polymyxin B and colistin, which target only gram-negative bacteria, daptomycin specifically targets gram-positive bacteria. It is typically administered intravenously and seems to be well tolerated, showing reversible toxicity in skeletal muscles.

Drugs That Inhibit Bacterial Membrane Function

| Mechanism of Action | Drug Class | Specific Drugs | Spectrum of Activity | Clinical Use |
|---|---|---|---|---|
| Interacts with lipopolysaccharide in the outer membrane of gram-negative bacteria, killing the cell through the eventual disruption of the outer membrane and cytoplasmic membrane | Polymyxins | Polymyxin B | Narrow spectrum against gram-negative bacteria, including multidrug-resistant strains | Topical preparations to prevent infections in wounds |
| | | Polymyxin E (colistin) | Narrow spectrum against gram-negative bacteria, including multidrug-resistant strains | Oral dosing to decontaminate bowels to prevent infections in immunocompromised patients or patients undergoing invasive surgery/procedures. |
| | | | | Intravenous dosing to treat serious systemic infections caused by multidrug-resistant pathogens |
| Inserts into the cytoplasmic membrane of gram-positive bacteria, disrupting the membrane and killing the cell | Lipopeptide | Daptomycin | Narrow spectrum against gram-positive bacteria, including multidrug-resistant strains | Complicated skin and skin-structure infections and bacteremia caused by gram-positive pathogens, including MRSA |

***Table*** 9.3.4

check your understanding

- How do polymyxins inhibit membrane function?

## Inhibitors of Nucleic Acid Synthesis

Some antibacterial drugs work by inhibiting nucleic acid synthesis (***Table*** 9.3.5). For example, **metronidazole** is a semisynthetic member of the nitroimidazole family that is also an antiprotozoan. It interferes with DNA replication in target cells. The drug **rifampin** is a semisynthetic member of the rifamycin family and functions by blocking RNA polymerase activity in bacteria. The RNA polymerase enzymes in bacteria are structurally different from those in eukaryotes, providing for selective toxicity against bacterial cells. It is used for the treatment of a variety of infections, but its primary use, often in a cocktail with other antibacterial drugs, is against mycobacteria that cause tuberculosis. Despite the selectivity of its mechanism, rifampin can induce liver enzymes to increase metabolism of other drugs being administered (antagonism), leading to hepatotoxicity (liver toxicity) and negatively influencing the bioavailability and therapeutic effect of the companion drugs.

One member of the quinolone family, a group of synthetic antimicrobials, is **nalidixic acid**. It was discovered in 1962 as a byproduct during the synthesis of chloroquine, an antimalarial drug. Nalidixic acid selectively inhibits the activity of bacterial DNA gyrase, blocking DNA replication. Chemical modifications to the original quinolone backbone have resulted in the production of **fluoroquinolones**, like ciprofloxacin and levofloxacin, which also inhibit the activity of DNA gyrase. Ciprofloxacin and levofloxacin are effective against a broad spectrum of gram-positive or gram-negative bacteria, and are among the most commonly prescribed antibiotics used to treat a wide range of infections, including urinary tract infections, respiratory infections, abdominal

infections, and skin infections. However, despite their selective toxicity against DNA gyrase, side effects associated with different fluoroquinolones include phototoxicity, neurotoxicity, cardiotoxicity, glucose metabolism dysfunction, and increased risk for tendon rupture.

**Drugs That Inhibit Bacterial Nucleic Acid Synthesis**

| Mechanisms of Action | Drug Class | Specific Drugs | Spectrum of activity | Clinical Use |
|---|---|---|---|---|
| Inhibits bacterial RNA polymerase activity and blocks transcription, killing the cell | Rifamycin | Rifampin | Narrow spectrum with activity against gram-positive and limited numbers of gram-negative bacteria. Also active against *Mycobacterium tuberculosis*. | Combination therapy for treatment of tuberculosis |
| Inhibits the activity of DNA gyrase and blocks DNA replication, killing the cell | Fluoroquinolones | Ciprofloxacin, ofloxacin, moxifloxacin | Broad spectrum against gram-positive and gram-negative bacteria | Wide variety of skin and systemic infections |

***Table*** 9.3.5

check your understanding

- Why do inhibitors of bacterial nucleic acid synthesis not target host cells?

## Inhibitors of Metabolic Pathways

Some synthetic drugs control bacterial infections by functioning as **antimetabolites**, competitive inhibitors for bacterial metabolic enzymes (***Table*** 9.3.6). The **sulfonamides** (**sulfa drugs**) are the oldest synthetic antibacterial agents and are structural analogues of *para*-aminobenzoic acid (PABA), an early intermediate in folic acid synthesis (***Figure*** 9.3.4). By inhibiting the enzyme involved in the production of dihydrofolic acid, sulfonamides block bacterial biosynthesis of folic acid and, subsequently, pyrimidines and purines required for nucleic acid synthesis. This mechanism of action provides bacteriostatic inhibition of growth against a wide spectrum of gram-positive and gram-negative pathogens. Because humans obtain folic acid from food instead of synthesizing it intracellularly, sulfonamides are selectively toxic for bacteria. However, allergic reactions to sulfa drugs are common. The sulfones are structurally similar to sulfonamides but are not commonly used today except for the treatment of Hansen's disease (leprosy).

Trimethoprim is a synthetic antimicrobial compound that serves as an antimetabolite within the same folic acid synthesis pathway as sulfonamides. **However**, trimethoprim is a structural analogue of dihydrofolic acid and inhibits a later step in the metabolic pathway (***Figure*** 9.3.4). Trimethoprim is used in combination with the sulfa drug sulfamethoxazole to treat urinary tract infections, ear infections, and bronchitis. As discussed, the combination of trimethoprim and sulfamethoxazole is an example of antibacterial synergy. When used alone, each antimetabolite only decreases production of folic acid to a level where bacteriostatic inhibition of growth occurs. However, when used in combination, inhibition of both steps in the metabolic pathway decreases folic acid synthesis to a level that is lethal to the bacterial cell. Because of the importance of folic acid during fetal development, sulfa drugs and trimethoprim use should be carefully considered during early pregnancy.

The drug **isoniazid** is an antimetabolite with specific toxicity for mycobacteria and has long been used in combination with rifampin or streptomycin in the treatment of tuberculosis. It is administered as a prodrug, requiring activation through the action of an intracellular bacterial peroxidase enzyme, forming isoniazid-nicotinamide adenine dinucleotide (NAD) and isoniazid-nicotinamide adenine dinucleotide phosphate (NADP), ultimately preventing the synthesis of mycolic acid, which is essential for mycobacterial cell walls. Possible side effects of isoniazid use include hepatotoxicity, neurotoxicity, and hematologic toxicity (anemia).

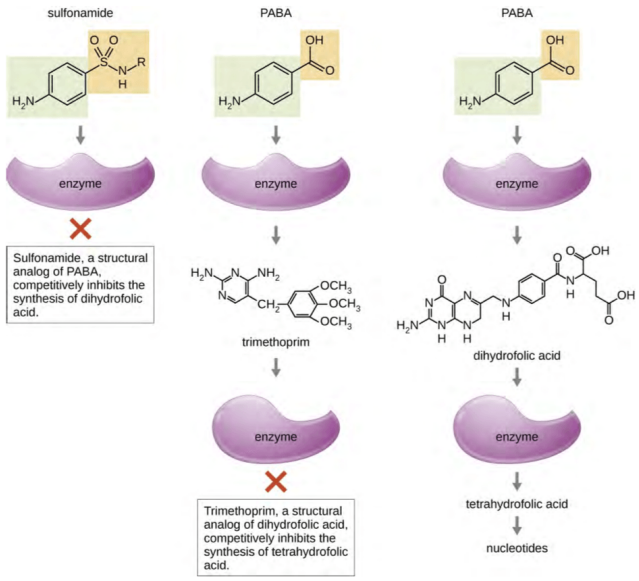



***Figure*** 9.3.4 *Sulfonamides and trimethoprim are examples of antimetabolites that interfere in the bacterial synthesis of folic acid by blocking purine and pyrimidine biosynthesis, thus inhibiting bacterial growth.*

**Antimetabolite Drugs**

| Metabolic Pathway Target | Mechanism of Action | Drug Class | Specific Drugs | Spectrum of Activity |
|---|---|---|---|---|
| Folic acid synthesis | Inhibits the enzyme involved in production of dihydrofolic acid | Sulfonamides | Sulfamethoxazole | Broad spectrum against gram-positive and gram-negative bacteria |
| | | Sulfones | Dapsone | |
| | Inhibits the enzyme involved in the production of tetrahydrofolic acid | Not applicable | Trimethoprim | Broad spectrum against gram-positive and gram-negative bacteria |

| Metabolic Pathway Target | Mechanism of Action | Drug Class | Specific Drugs | Spectrum of Activity |
|---|---|---|---|---|
| Mycolic acid synthesis | Interferes with the synthesis of mycolic acid | Not applicable | Isoniazid | Narrow spectrum against *Mycobacterium* spp., including *M. tuberculosis* |

***Table*** 9.3.6

check your understanding

- How do sulfonamides and trimethoprim selectively target bacteria?

## Inhibitor of ATP Synthase

Bedaquiline, representing the synthetic antibacterial class of compounds called the diarylquinolones, uses a novel mode of action that specifically inhibits mycobacterial growth. Although the specific mechanism has yet to be elucidated, this compound appears to interfere with the function of ATP synthases, perhaps by interfering with the use of the hydrogen ion gradient for ATP synthesis by oxidative phosphorylation, leading to reduced ATP production. Due to its side effects, including hepatotoxicity and potentially lethal heart arrhythmia, its use is reserved for serious, otherwise untreatable cases of tuberculosis.

link to learning




To learn more about the general principles of antimicrobial therapy and bacterial modes of action,

visit Michigan State University's Antimicrobial Resistance Learning Site (https://openstax.org/l/22MSUantireslea) , particularly pages 6 through 9.

Clinical Focus

**Part 2**

Reading thorough Marisa's health history, the doctor noticed that during her hospitalization in Vietnam, she was catheterized and received the antimicrobial drugs ceftazidime and metronidazole. Upon learning this, the doctor ordered a CT scan of Marisa's abdomen to rule out appendicitis; the doctor also requested blood work to see if she had an elevated white blood cell count, and ordered a urine analysis test and urine culture to look for the presence of white blood cells, red blood cells, and bacteria.

Marisa's urine sample came back positive for the presence of bacteria, indicating a urinary tract infection (UTI). The doctor prescribed ciprofloxacin. In the meantime, her urine was cultured to grow the bacterium for further testing.

- What types of antimicrobials are typically prescribed for UTIs?
- Based upon the antimicrobial drugs she was given in Vietnam, which of the antimicrobials for treatment of a UTI would you predict to be ineffective?

*Jump to the next Clinical Focus box. Go back to the previous Clinical Focus box.*

## Summary

- Antibacterial compounds exhibit **selective toxicity**, largely due to differences between prokaryotic and eukaryotic cell structure.
- Cell wall synthesis inhibitors, including the **β-lactams**, the **glycopeptides**, and **bacitracin**, interfere with peptidoglycan synthesis, making bacterial cells more prone to osmotic lysis.
- There are a variety of broad-spectrum, bacterial protein synthesis inhibitors that selectively target the prokaryotic 70S ribosome, including those that bind to the 30S subunit (**aminoglycosides** and **tetracyclines**) and others that bind to the 50S subunit (**macrolides**, **lincosamides**, **chloramphenicol**, and **oxazolidinones**).
- **Polymyxins** are lipophilic polypeptide antibiotics that target the lipopolysaccharide component of gram- negative bacteria and ultimately disrupt the integrity of the outer and inner membranes of these bacteria.

- The nucleic acid synthesis inhibitors rifamycins and **fluoroquinolones** target bacterial RNA transcription and DNA replication, respectively.
- Some antibacterial drugs are **antimetabolites**, acting as competitive inhibitors for bacterial metabolic enzymes. **Sulfonamides** and **trimethoprim** are antimetabolites that interfere with bacterial folic acid synthesis. **Isoniazid** is an antimetabolite that interferes with mycolic acid synthesis in mycobacteria.

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# 9.4: Mechanisms of Other Antimicrobial Drugs

**Learning Objectives**

- Explain the differences between modes of action of drugs that target fungi, protozoa, helminths, and viruses

Because fungi, protozoa, and helminths are eukaryotic, their cells are very similar to human cells, making it more difficult to develop drugs with selective toxicity. Additionally, viruses replicate within human host cells, making it difficult to develop drugs that are selectively toxic to viruses or virus-infected cells. Despite these challenges, there are antimicrobial drugs that target fungi, protozoa, helminths, and viruses, and some even target more than one type of microbe. Table 9.4.1, Table 9.4.2, Table 9.4.3, and Table 9.4.4 provide examples for antimicrobial drugs in these various classes.

## Antifungal Drugs

The most common mode of action for antifungal drugs is the disruption of the cell membrane. Antifungals take advantage of small differences between fungi and humans in the biochemical pathways that synthesize sterols. The sterols are important in maintaining proper membrane fluidity and, hence, proper function of the cell membrane. For most fungi, the predominant membrane sterol is ergosterol. Because human cell membranes use cholesterol, instead of ergosterol, antifungal drugs that target ergosterol synthesis are selectively toxic (Figure 9.4.1).

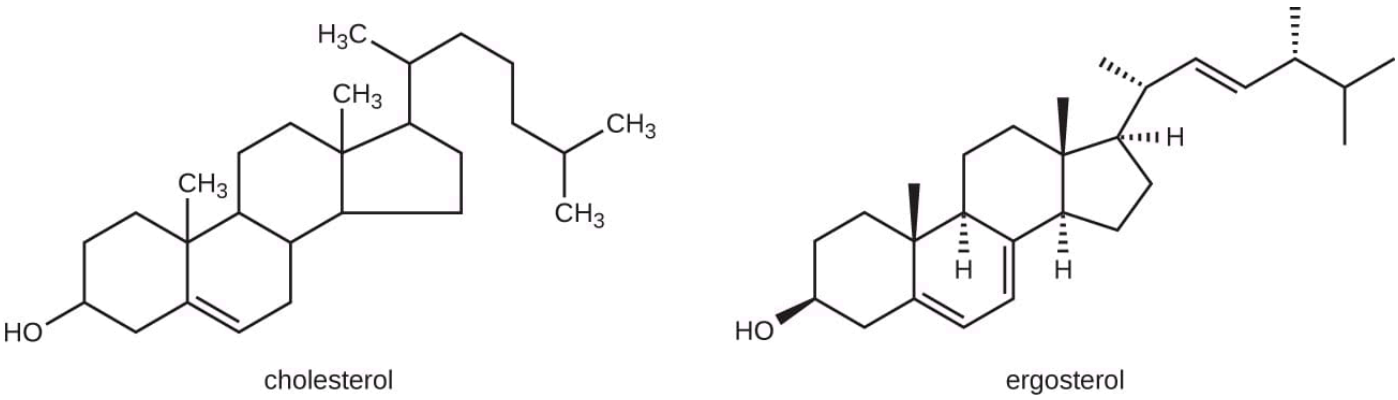



Figure 9.4.1: The predominant sterol found in human cells is cholesterol, whereas the predominant sterol found in fungi is ergosterol, making ergosterol a good target for antifungal drug development.

The imidazoles are synthetic fungicides that disrupt ergosterol biosynthesis; they are commonly used in medical applications and also in agriculture to keep seeds and harvested crops from molding. Examples include miconazole, ketoconazole, and clotrimazole, which are used to treat fungal skin infections such as ringworm, specifically tinea pedis (athlete's foot), tinea cruris (jock itch), and tinea corporis. These infections are commonly caused by dermatophytes of the genera *Trichophyton*, *Epidermophyton*, and *Microsporum*. Miconazole is also used predominantly for the treatment of vaginal yeast infections caused by the fungus *Candida*, and ketoconazole is used for the treatment of tinea versicolor and dandruff, which both can be caused by the fungus *Malassezia*.

The triazole drugs, including fluconazole, also inhibit ergosterol biosynthesis. However, they can be administered orally or intravenously for the treatment of several types of systemic yeast infections, including oral thrush and cryptococcal meningitis, both of which are prevalent in patients with AIDS. The triazoles also exhibit more selective toxicity, compared with the imidazoles, and are associated with fewer side effects.

The allylamines, a structurally different class of synthetic antifungal drugs, inhibit an earlier step in ergosterol biosynthesis. The most commonly used allylamine is terbinafine (marketed under the brand name Lamisil), which is used topically for the treatment of dermatophytic skin infections like athlete's foot, ringworm, and jock itch. Oral treatment with terbinafine is also used for the treatment of fingernail and toenail fungus, but it can be associated with the rare side effect of hepatotoxicity.

The polyenes are a class of antifungal agents naturally produced by certain actinomycete soil bacteria and are structurally related to macrolides. These large, lipophilic molecules bind to ergosterol in fungal cytoplasmic membranes, thus creating pores. Common examples include nystatin and amphotericin B. Nystatin is typically used as a topical treatment for yeast infections of the skin, mouth, and vagina, but may also be used for intestinal fungal infections. The drug amphotericin B is used for systemic fungal infections like aspergillosis, cryptococcal meningitis, histoplasmosis, blastomycosis, and candidiasis. Amphotericin B was the only antifungal drug available for several decades, but its use is associated with some serious side effects, including nephrotoxicity (kidney toxicity).

Amphotericin B is often used in combination with flucytosine, a fluorinated pyrimidine analog that is converted by a fungal-specific enzyme into a toxic product that interferes with both DNA replication and protein synthesis in fungi. Flucytosine is also associated with hepatotoxicity (liver toxicity) and bone marrow depression.

Beyond targeting ergosterol in fungal cell membranes, there are a few antifungal drugs that target other fungal structures (Figure 9.4.2). The echinocandins, including caspofungin, are a group of naturally produced antifungal compounds that block the synthesis of β(1→3) glucan found in fungal cell walls but not found in human cells. This drug class has the nickname “penicillin for fungi.” Caspofungin is used for the treatment of aspergillosis as well as systemic yeast infections.

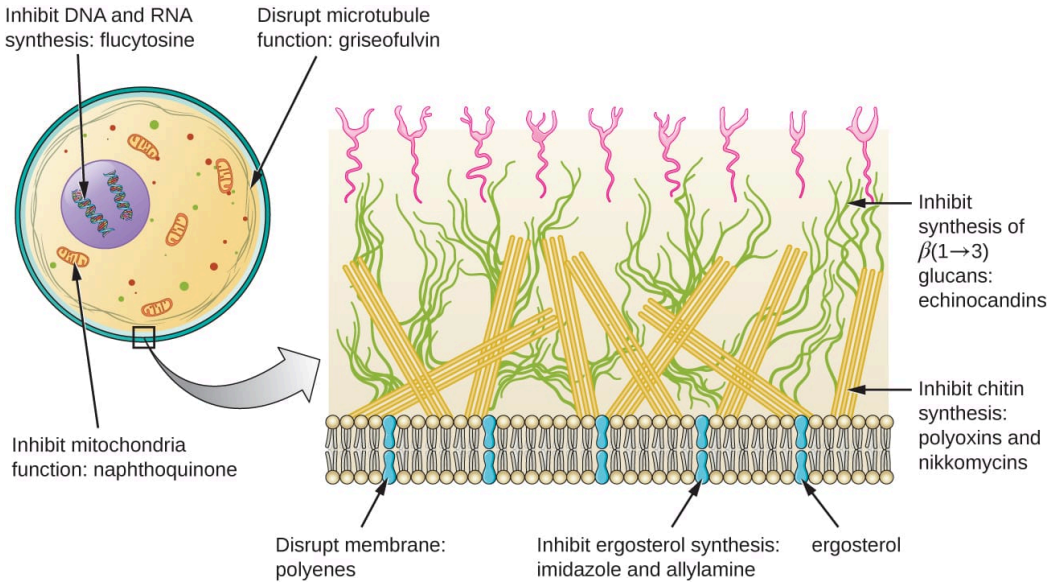



Figure 9.4.2: Antifungal drugs target several different cell structures. (credit right: modification of work by “Maya and Rike”/Wikimedia Commons)

Although chitin is only a minor constituent of fungal cell walls, it is also absent in human cells, making it a selective target. The polyoxins and nikkomycins are naturally produced antifungals that target chitin synthesis. Polyoxins are used to control fungi for agricultural purposes, and nikkomycin Z is currently under development for use in humans to treat yeast infections and Valley fever (coccidioidomycosis), a fungal disease prevalent in the southwestern US.[1]

The naturally produced antifungal griseofulvin is thought to specifically disrupt fungal cell division by interfering with microtubules involved in spindle formation during mitosis. It was one of the first antifungals, but its use is associated with hepatotoxicity. It is typically administered orally to treat various types of dermatophytic skin infections when other topical antifungal treatments are ineffective.

There are a few drugs that act as antimetabolites against fungal processes. For example, atovaquone, a representative of the naphthoquinone drug class, is a semisynthetic antimetabolite for fungal and protozoal versions of a mitochondrial cytochrome important in electron transport. Structurally, it is an analog of coenzyme Q, with which it competes for electron binding. It is particularly useful for the treatment of *Pneumocystis* pneumonia caused by *Pneumocystis jirovecii*. The antibacterial sulfamethoxazole-trimethoprim combination also acts as an antimetabolite against *P. jirovecii*.

Table 9.4.1 shows the various therapeutic classes of antifungal drugs, categorized by mode of action, with examples of each.

*Table 9.4.1: Common Antifungal Drugs*

| Mechanism of Action | Drug Class | Specific Drugs | Clinical Uses |
|---|---|---|---|
| Inhibit ergosterol synthesis | Imidazoles | Miconazole, ketoconazole, clotrimazole | Fungal skin infections and vaginal yeast infections |
| | Triazoles | Fluconazole | Systemic yeast infections, oral thrush, and cryptococcal meningitis |
| | Allylamines | Terbinafine | Dermatophytic skin infections (athlete's foot, ring worm, jock itch), and infections of fingernails and toenails |
| Bind ergosterol in the cell membrane and create pores that disrupt the membrane | Polyenes | Nystatin | Used topically for yeast infections of skin, mouth, and vagina; also used for fungal infections of the intestine |
| | | Amphotericin B | Variety systemic fungal infections |
| Inhibit cell wall synthesis | Echinocandins | Caspofungin | Aspergillosis and systemic yeast infections |
| | Not applicable | Nikkomycin Z | Coccidioidomycosis (Valley fever) and yeast infections |
| Inhibit microtubules and cell division | Not applicable | Griseofulvin | Dermatophytic skin infections |

## Exercise 9.4.1

How is disruption of ergosterol biosynthesis an effective mode of action for antifungals?

## Treating a Fungal Infection of the Lungs

Jack, a 48-year-old engineer, is HIV positive but generally healthy thanks to antiretroviral therapy (ART). However, after a particularly intense week at work, he developed a fever and a dry cough. He assumed that he just had a cold or mild flu due to overexertion and didn't think much of it. However, after about a week, he began to experience fatigue, weight loss, and shortness of breath. He decided to visit his physician, who found that Jack had a low level of blood oxygenation. The physician ordered blood testing, a chest X-ray, and the collection of an induced sputum sample for analysis. His X-ray showed a fine cloudiness and several pneumatoceles (thin-walled pockets of air), which indicated *Pneumocystis* pneumonia (PCP), a type of pneumonia caused by the fungus *Pneumocystis jirovecii*. Jack's physician admitted him to the hospital and prescribed Bactrim, a combination of sulfamethoxazole and trimethoprim, to be administered intravenously.

*P. jirovecii* is a yeast-like fungus with a life cycle similar to that of protozoans. As such, it was classified as a protozoan until the 1980s. It lives only in the lung tissue of infected persons and is transmitted from person to person, with many people exposed as children. Typically, *P. jirovecii* only causes pneumonia in immunocompromised individuals. Healthy people may carry the fungus in their lungs with no symptoms of disease. PCP is particularly problematic among HIV patients with compromised immune systems.

PCP is usually treated with oral or intravenous Bactrim, but atovaquone or pentamidine(another antiparasitic drug) are alternatives. If not treated, PCP can progress, leading to a collapsed lung and nearly 100% mortality. Even with antimicrobial drug therapy, PCP still is responsible for 10% of HIV-related deaths.

The cytological examination, using direct immunofluorescence assay (DFA), of a smear from Jack's sputum sample confirmed the presence of *P. jirovecii* (Figure 9.4.3). Additionally, the results of Jack's blood tests revealed that his white blood cell count had dipped, making him more susceptible to the fungus. His physician reviewed his ART regimen and made adjustments. After a few days of hospitalization, Jack was released to continue his antimicrobial therapy at home. With the adjustments to his ART therapy, Jack's CD4 counts began to increase and he was able to go back to work.

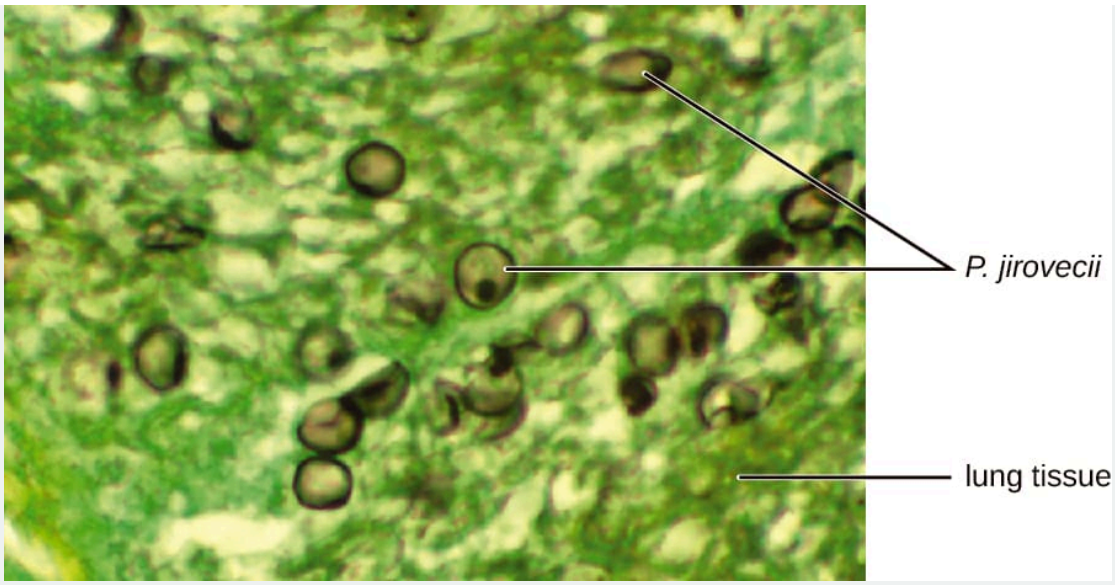



Figure 9.4.3: Microscopic examination of an induced sputum sample or bronchoaveolar lavage sample typically reveals the organism, as shown here. (credit: modification of work by the Centers for Disease Control and Prevention)

## Antiprotozoan Drugs

There are a few mechanisms by which antiprotozoan drugs target infectious protozoans (Table 9.4.3). Some are antimetabolites, such as atovaquone, proguanil, and artemisinins. Atovaquone, in addition to being antifungal, blocks electron transport in protozoans and is used for the treatment of protozoan infections including malaria, babesiosis, and toxoplasmosis. Proguanil is another synthetic antimetabolite that is processed in parasitic cells into its active form, which inhibits protozoan folic acid synthesis. It is often used in combination with atovaquone, and the combination is marketed as Malarone for both malaria treatment and prevention.

Artemisinin, a plant-derived antifungal first discovered by Chinese scientists in the 1970s, is quite effective against malaria. Semisynthetic derivatives of artemisinin are more water soluble than the natural version, which makes them more bioavailable. Although the exact mechanism of action is unclear, artemisinins appear to act as prodrugs that are metabolized by target cells to produce reactive oxygen species (ROS) that damage target cells. Due to the rise in resistance to antimalarial drugs, artemisinins are also commonly used in combination with other antimalarial compounds in artemisinin-based combination therapy (ACT).

Several antimetabolites are used for the treatment of toxoplasmosis caused by the parasite *Toxoplasma gondii*. The synthetic sulfa drug sulfadiazine competitively inhibits an enzyme in folic acid production in parasites and can be used to treat malaria and toxoplasmosis. Pyrimethamine is a synthetic drug that inhibits a different enzyme in the folic acid production pathway and is often used in combination with sulfadoxine (another sulfa drug) for the treatment of malariaor in combination with sulfadiazine for the treatment of toxoplasmosis. Side effects of pyrimethamine include decreased bone marrow activity that may cause increased bruising and low red blood cell counts. When toxicity is a concern, spiramycin, a macrolide protein synthesis inhibitor, is typically administered for the treatment of toxoplasmosis.

Two classes of antiprotozoan drugs interfere with nucleic acid synthesis: nitroimidazoles and quinolines. Nitroimidazoles, including semisynthetic metronidazole, which was discussed previously as an antibacterial drug, and synthetic tinidazole, are useful in combating a wide variety of protozoan pathogens, such as *Giardia lamblia*, *Entamoeba histolytica*, and *Trichomonas vaginalis*. Upon introduction into these cells in low-oxygen environments, nitroimidazoles become activated and introduce DNA strand breakage, interfering with DNA replication in target cells. Unfortunately, metronidazole is associated with carcinogenesis (the development of cancer) in humans.

Another type of synthetic antiprotozoan drug that has long been thought to specifically interfere with DNA replication in certain pathogens is pentamidine. It has historically been used for the treatment of African sleeping sickness (caused by the protozoan *Trypanosoma brucei*) and leishmaniasis (caused by protozoa of the genus *Leishmania*), but it is also an alternative treatment for the fungus *Pneumocystis*. Some studies indicate that it specifically binds to the DNA found within kinetoplasts (kDNA; long mitochondrion-like structures unique to trypanosomes), leading to the cleavage of kDNA. However, nuclear DNA of both the parasite and host remain unaffected. It also appears to bind to tRNA, inhibiting the addition of amino acids to tRNA, thus

preventing protein synthesis. Possible side effects of pentamidine use include pancreatic dysfunction and liver damage.

The quinolines are a class of synthetic compounds related to quinine, which has a long history of use against malaria. Quinolines are thought to interfere with heme detoxification, which is necessary for the parasite's effective breakdown of hemoglobin into amino acids inside red blood cells. The synthetic derivatives chloroquine, quinacrine (also called mepacrine), and mefloquine are commonly used as antimalarials, and chloroquine is also used to treat amebiasis typically caused by *Entamoeba histolytica*. Long-term prophylactic use of chloroquine or mefloquine may result in serious side effects, including hallucinations or cardiac issues. Patients with glucose-6-phosphate dehydrogenase deficiency experience severe anemia when treated with chloroquine.

*Table 9.4.2: Common Antiprotozoan Drugs*

| Mechanism of Action | Drug Class | Specific Drugs | Clinical Uses |
|---|---|---|---|
| Inhibit electron transport in mitochondria | Naphthoquinone | Atovaquone | Malaria, babesiosis, and toxoplasmosis |
| Inhibit folic acid synthesis | Not applicable | Proquanil | Combination therapy with atovaquone for malaria treatment and prevention |
| | Sulfonamide | Sulfadiazine | Malaria and toxoplasmosis |
| | Not applicable | Pyrimethamine | Combination therapy with sulfadoxine (sulfa drug) for malaria |
| Produces damaging reactive oxygen species | Not applicable | Artemisinin | Combination therapy to treat malaria |
| Inhibit DNA synthesis | Nitroimidazoles | Metronidazole, tinidazole | Infections caused by *Giardia lamblia, Entamoeba histolytica,* and *Trichomonas vaginalis* |
| | Not applicable | Pentamidine | African sleeping sickness and leishmaniasis |
| Inhibit heme detoxification | Quinolines | Chloroquine | Malaria and infections with *E. histolytica* |
| | | Mepacrine, mefloquine | Malaria |

**Exercise 9.4.2**

List two modes of action for antiprotozoan drugs.

## Antihelminthic Drugs

Because helminths are multicellular eukaryotes like humans, developing drugs with selective toxicity against them is extremely challenging. Despite this, several effective classes have been developed (Table 9.4.3). Synthetic benzimidazoles, like mebendazole and albendazole, bind to helminthic β-tubulin, preventing microtubule formation. Microtubules in the intestinal cells of the worms seem to be particularly affected, leading to a reduction in glucose uptake. Besides their activity against a broad range of helminths, benzimidazoles are also active against many protozoans, fungi, and viruses, and their use for inhibiting mitosis and cell cycle progression in cancer cells is under study.[2] Possible side effects of their use include liver damage and bone marrow suppression.

The avermectins are members of the macrolide family that were first discovered from a Japanese soil isolate, *Streptomyces avermectinius*. A more potent semisynthetic derivative of avermectin is ivermectin, which binds to glutamate-gated chloride channels specific to invertebrates including helminths, blocking neuronal transmission and causing starvation, paralysis, and death of the worms. Ivermectin is used to treat roundworm diseases, including onchocerciasis (also called river blindness, caused by the worm *Onchocerca volvulus*) and strongyloidiasis (caused by the worm *Strongyloides stercoralis* or *S. fuelleborni*). Ivermectin also can also treat parasitic insects like mites, lice, and bed bugs, and is nontoxic to humans.

Niclosamide is a synthetic drug that has been used for over 50 years to treat tapeworm infections. Although its mode of action is not entirely clear, niclosamide appears to inhibit ATP formation under anaerobic conditions and inhibit oxidative phosphorylation in the mitochondria of its target pathogens. Niclosamide is not absorbed from the gastrointestinal tract, thus it can achieve high

localized intestinal concentrations in patients. Recently, it has been shown to also have antibacterial, antiviral, and antitumor activities.[345]

Another synthetic antihelminthic drug is praziquantel, which used for the treatment of parasitic tapeworms and liver flukes, and is particularly useful for the treatment of schistosomiasis (caused by blood flukes from three genera of *Schistosoma*). Its mode of action remains unclear, but it appears to cause the influx of calcium into the worm, resulting in intense spasm and paralysis of the worm. It is often used as a preferred alternative to niclosamide in the treatment of tapeworms when gastrointestinal discomfort limits niclosamide use.

The thioxanthenones, another class of synthetic drugs structurally related to quinine, exhibit antischistosomal activity by inhibiting RNA synthesis. The thioxanthenone lucanthone and its metabolite hycanthone were the first used clinically, but serious neurological, gastrointestinal, cardiovascular, and hepatic side effects led to their discontinuation. Oxamniquine, a less toxic derivative of hycanthone, is only effective against S. *mansoni*, one of the three species known to cause schistosomiasis in humans. Praziquantel was developed to target the other two schistosome species, but concerns about increasing resistance have renewed interest in developing additional derivatives of oxamniquine to target all three clinically important schistosome species.

*Table 9.4.3: Common Antihelminthic Drugs*

| Mechanism of Action | Drug Class | Specific Drugs | Clinical Uses |
|---|---|---|---|
| Inhibit microtubule formation, reducing glucose uptake | Benzimidazoles | Mebendazole, albendazole | Variety of helminth infections |
| Block neuronal transmission, causing paralysis and starvation | Avermectins | Ivermectin | Roundworm diseases, including river blindness and strongyloidiasis, and treatment of parasitic insects |
| Inhibit ATP production | Not applicable | Niclosamide | Intestinal tapeworm infections |
| Induce calcium influx | Not applicable | Praziquantel | Schistosomiasis (blood flukes) |
| Inhibit RNA synthesis | Thioxanthenones | Lucanthone, hycanthone, oxamniquine | Schistosomiasis (blood flukes) |

**Exercise 9.4.3**

Why are antihelminthic drugs difficult to develop?

## Antiviral Drugs

Unlike the complex structure of fungi, protozoa, and helminths, viral structure is simple, consisting of nucleic acid, a protein coat, viral enzymes, and, sometimes, a lipid envelope. Furthermore, viruses are obligate intracellular pathogens that use the host's cellular machinery to replicate. These characteristics make it difficult to develop drugs with selective toxicity against viruses.

Many antiviral drugs are nucleoside analogs and function by inhibiting nucleic acid biosynthesis. For example, acyclovir(marketed as Zovirax) is a synthetic analog of the nucleoside guanosine (Figure 9.4.4). It is activated by the herpes simplex viral enzyme thymidine kinase and, when added to a growing DNA strand during replication, causes chain termination. Its specificity for virus-infected cells comes from both the need for a viral enzyme to activate it and the increased affinity of the activated form for viral DNA polymerase compared to host cell DNA polymerase. Acyclovir and its derivatives are frequently used for the treatment of herpes virus infections, including genital herpes, chickenpox, shingles, Epstein-Barr virus infections, and cytomegalovirus infections. Acyclovir can be administered either topically or systemically, depending on the infection. One possible side effect of its use includes nephrotoxicity. The drug adenine-arabinoside, marketed as vidarabine, is a synthetic analog to deoxyadenosine that has a mechanism of action similar to that of acyclovir. It is also effective for the treatment of various human herpes viruses. However, because of possible side effects involving low white blood cell counts and neurotoxicity, treatment with acyclovir is now preferred.

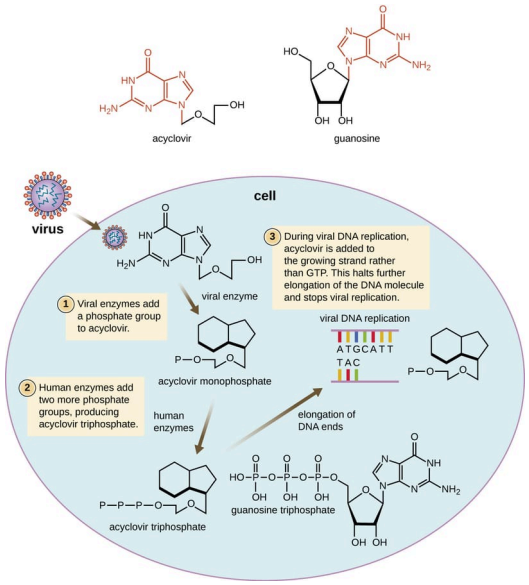



Figure 9.4.4: Acyclovir is a structural analog of guanosine. It is specifically activated by the viral enzyme thymidine kinase and then preferentially binds to viral DNA polymerase, leading to chain termination during DNA replication.

Ribavirin, another synthetic guanosine analog, works by a mechanism of action that is not entirely clear. It appears to interfere with both DNA and RNA synthesis, perhaps by reducing intracellular pools of guanosine triphosphate (GTP). Ribavarin also appears to inhibit the RNA polymerase of hepatitis C virus. It is primarily used for the treatment of the RNA viruses like hepatitis C (in combination therapy with interferon) and respiratory syncytial virus. Possible side effects of ribavirin use include anemia and developmental effects on unborn children in pregnant patients. In recent years, another nucleotide analog, sofosbuvir (Solvaldi), has also been developed for the treatment of hepatitis C. Sofosbuvir is a uridine analog that interferes with viral polymerase activity. It is commonly coadministered with ribavirin, with and without interferon.

Inhibition of nucleic acid synthesis is not the only target of synthetic antivirals. Although the mode of action of amantadine and its relative rimantadine are not entirely clear, these drugs appear to bind to a transmembrane protein that is involved in the escape of the influenza virus from endosomes. Blocking escape of the virus also prevents viral RNA release into host cells and subsequent viral replication. Increasing resistance has limited the use of amantadine and rimantadine in the treatment of influenza A. Use of amantadine can result in neurological side effects, but the side effects of rimantadine seem less severe. Interestingly, because of their effects on brain chemicals such as dopamine and NMDA (N-methyl D-aspartate), amantadine and rimantadine are also used for the treatment of Parkinson's disease.

Neuraminidase inhibitors, including olsetamivir (Tamiflu), zanamivir (Relenza), and peramivir (Rapivab), specifically target influenza viruses by blocking the activity of influenza virus neuraminidase, preventing the release of the virus from infected cells. These three antivirals can decrease flu symptoms and shorten the duration of illness, but they differ in their modes of administration: olsetamivir is administered orally, zanamivir is inhaled, and peramivir is administered intravenously. Resistance to these neuraminidase inhibitors still seems to be minimal.

Pleconaril is a synthetic antiviral under development that showed promise for the treatment of picornaviruses. Use of pleconaril for the treatment of the common cold caused by rhinoviruses was not approved by the FDA in 2002 because of lack of proven effectiveness, lack of stability, and association with irregular menstruation. Its further development for this purpose was halted in 2007. However, pleconaril is still being investigated for use in the treatment of life-threatening complications of enteroviruses, such as meningitis and sepsis. It is also being investigated for use in the global eradication of a specific enterovirus, polio.[6] Pleconaril seems to work by binding to the viral capsid and preventing the uncoating of viral particles inside host cells during viral infection.

Viruses with complex life cycles, such as HIV, can be more difficult to treat. First, HIV targets CD4-positive white blood cells, which are necessary for a normal immune response to infection. Second, HIV is a retrovirus, meaning that it converts its RNA genome into a DNA copy that integrates into the host cell's genome, thus hiding within host cell DNA. Third, the HIV reverse transcriptase lacks proofreading activity and introduces mutations that allow for rapid development of antiviral drug resistance. To help prevent the emergence of resistance, a combination of specific synthetic antiviral drugs is typically used in ART for HIV (Figure 9.4.5).

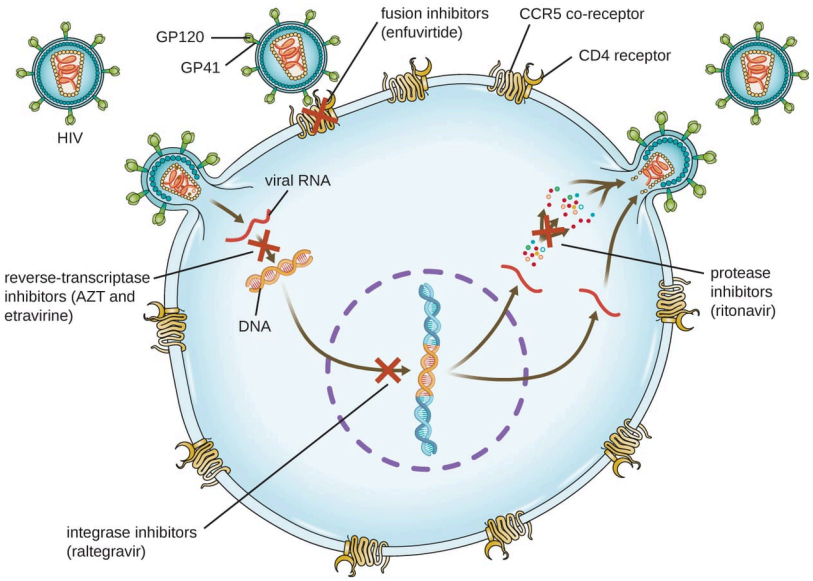



Figure 9.4.5: Antiretroviral therapy (ART) is typically used for the treatment of HIV. The targets of drug classes currently in use are shown here. (credit: modification of work by Thomas Splettstoesser)

The reverse transcriptase inhibitors block the early step of converting viral RNA genome into DNA, and can include competitive nucleoside analog inhibitors (e.g., azidothymidine/zidovudine, or AZT) and non-nucleoside noncompetitive inhibitors (e.g., etravirine) that bind reverse transcriptase and cause an inactivating conformational change. Drugs called protease inhibitors (e.g., ritonavir) block the processing of viral proteins and prevent viral maturation. Protease inhibitors are also being developed for the treatment of other viral types.[7] For example, simeprevir (Olysio) has been approved for the treatment of hepatitis C and is administered with ribavirin and interferon in combination therapy. The integrase inhibitors (e.g., raltegravir), block the activity of the HIV integrase responsible for the recombination of a DNA copy of the viral genome into the host cell chromosome. Additional drug classes for HIV treatment include the CCR5 antagonists and the fusion inhibitors (e.g., enfuviritide), which prevent the binding of HIV to the host cell coreceptor (chemokine receptor type 5 [CCR5]) and the merging of the viral envelope with the host cell membrane, respectively. Table 9.4.4 shows the various therapeutic classes of antiviral drugs, categorized by mode of action, with examples of each.

*Table 9.4.4: Common Antiviral Drugs*

| Mechanism of Action | Drug | Clinical Uses |
|---|---|---|
| Nucleoside analog inhibition of nucleic acid synthesis | Acyclovir | Herpes virus infections |
| | Azidothymidine/zidovudine (AZT) | HIV infections |
| | Ribavirin | Hepatitis C virus and respiratory syncytial virus infections |
| | Vidarabine | Herpes virus infections |
| | Sofosbuvir | Hepatitis C virus infections |
| Non-nucleoside noncompetitive inhibition | Etravirine | HIV infections |
| Inhibit escape of virus from endosomes | Amantadine, rimantadine | Infections with influenza virus |
| Inhibit neuraminadase | Olsetamivir, zanamivir, peramivir | Infections with influenza virus |
| Inhibit viral uncoating | Pleconaril | Serious enterovirus infections |
| Inhibition of protease | Ritonavir | HIV infections |
| | Simeprevir | Hepatitis C virus infections |
| Inhibition of integrase | Raltegravir | HIV infections |

| Mechanism of Action | Drug | Clinical Uses |
|---|---|---|
| Inhibition of membrane fusion | Enfuviritide | HIV infections |

**Exercise 9.4.4**

Why is HIV difficult to treat with antivirals?

**Link to Learning**

To learn more about the various classes of antiretroviral drugs used in the ART of HIV infection, explore each of the drugs in the HIV drug classes provided by US Department of Health and Human Services at this website.

## Key Concepts and Summary

- Because fungi, protozoans, and helminths are eukaryotic organisms like human cells, it is more challenging to develop antimicrobial drugs that specifically target them. Similarly, it is hard to target viruses because human viruses replicate inside of human cells.
- **Antifungal drugs** interfere with ergosterol synthesis, bind to ergosterol to disrupt fungal cell membrane integrity, or target cell wall-specific components or other cellular proteins.
- **Antiprotozoan drugs** increase cellular levels of reactive oxygen species, interfere with protozoal DNA replication (nuclear versus kDNA, respectively), and disrupt heme detoxification.
- **Antihelminthic drugs** disrupt helminthic and protozoan microtubule formation; block neuronal transmissions; inhibit anaerobic ATP formation and/or oxidative phosphorylation; induce a calcium influx in tapeworms, leading to spasms and paralysis; and interfere with RNA synthesis in schistosomes.
- **Antiviral drugs** inhibit viral entry, inhibit viral uncoating, inhibit nucleic acid biosynthesis, prevent viral escape from endosomes in host cells, and prevent viral release from infected cells.
- Because it can easily mutate to become drug resistant, HIV is typically treated with a combination of several **antiretroviral drugs**, which may include **reverse transcriptase inhibitors, protease inhibitors, integrase inhibitors**, and drugs that interfere with viral binding and fusion to initiate infection.

## Footnotes

1. 1 Centers for Disease Control and Prevention. “Valley Fever: Awareness Is Key.” www.cdc.gov/features/valleyfever/. Accessed June 1, 2016.
2. 2 B. Chu et al. “A Benzimidazole Derivative Exhibiting Antitumor Activity Blocks EGFR and HER2 Activity and Upregulates DR5 in Breast Cancer Cells.” *Cell Death and Disease* 6 (2015):e1686
3. 3 J.-X. Pan et al. “Niclosamide, An Old Antihelminthic Agent, Demonstrates Antitumor Activity by Blocking Multiple Signaling Pathways of Cancer Stem Cells.” *Chinese Journal of Cancer* 31 no. 4 (2012):178–184.
4. 4 F. Imperi et al. “New Life for an Old Drug: The Anthelmintic Drug Niclosamide Inhibits *Pseudomonas aeruginosa* Quorum Sensing.” *Antimicrobial Agents and Chemotherapy* 57 no. 2 (2013):996-1005.
5. 5 A. Jurgeit et al. “Niclosamide Is a Proton Carrier and Targets Acidic Endosomes with Broad Antiviral Effects.” *PLoS Pathogens* 8 no. 10 (2012):e1002976.
6. 6 M.J. Abzug. “The Enteroviruses: Problems in Need of Treatments.” *Journal of Infection* 68 no. S1 (2014):108–14.
7. 7 B.L. Pearlman. “Protease Inhibitors for the Treatment of Chronic Hepatitis C Genotype-1 Infection: The New Standard of Care.” *Lancet Infectious Diseases* 12 no. 9 (2012):717–728.

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# 9.5: Drug Resistance

**Learning Objectives**

- Explain the concept of drug resistance
- Describe how microorganisms develop or acquire drug resistance
- Describe the different mechanisms of antimicrobial drug resistance

Antimicrobial resistance is not a new phenomenon. In nature, microbes are constantly evolving in order to overcome the antimicrobial compounds produced by other microorganisms. Human development of antimicrobial drugs and their widespread clinical use has simply provided another selective pressure that promotes further evolution. Several important factors can accelerate the evolution of drug resistance. These include the overuse and misuse of antimicrobials, inappropriate use of antimicrobials, subtherapeutic dosing, and patient noncompliance with the recommended course of treatment.

Exposure of a pathogen to an antimicrobial compound can select for chromosomal mutations conferring resistance, which can be transferred vertically to subsequent microbial generations and eventually become predominant in a microbial population that is repeatedly exposed to the antimicrobial. Alternatively, many genes responsible for drug resistance are found on plasmids or in transposons that can be transferred easily between microbes through horizontal gene transfer (see How Asexual Prokaryotes Achieve Genetic Diversity). Transposons also have the ability to move resistance genes between plasmids and chromosomes to further promote the spread of resistance.

## Mechanisms for Drug Resistance

There are several common mechanisms for drug resistance, which are summarized in Figure 9.5.1. These mechanisms include enzymatic modification of the drug, modification of the antimicrobial target, and prevention of drug penetration or accumulation.

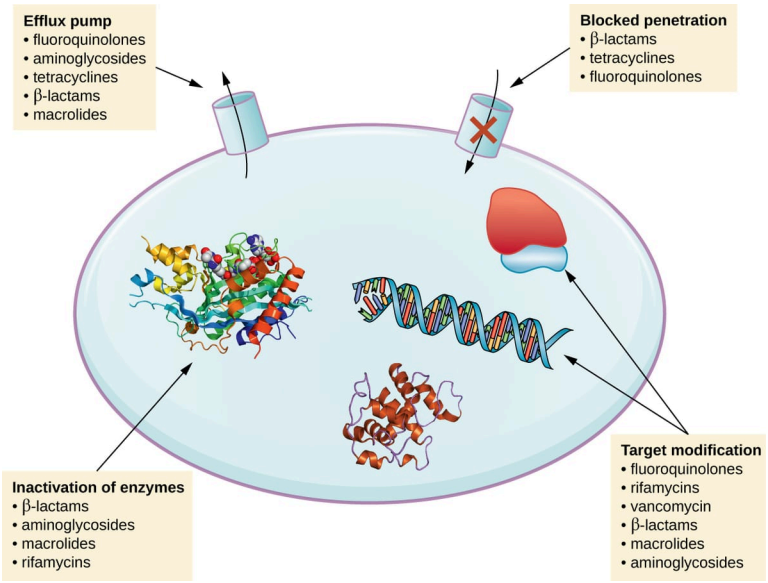



Figure 9.5.1: There are multiple strategies that microbes use to develop resistance to antimicrobial drugs. (Not shown: target overproduction, target mimicry, and enzymatic bypass). (credit: modification of work by Gerard D Wright)

## Drug Modification or Inactivation

Resistance genes may code for enzymes that chemically modify an antimicrobial, thereby inactivating it, or destroy an antimicrobial through hydrolysis. Resistance to many types of antimicrobials occurs through this mechanism. For example, aminoglycoside resistance can occur through enzymatic transfer of chemical groups to the drug molecule, impairing the binding

of the drug to its bacterial target. For β-lactams, bacterial resistance can involve the enzymatic hydrolysis of the β-lactam bond within the β-lactam ring of the drug molecule. Once the β-lactam bond is broken, the drug loses its antibacterial activity. This mechanism of resistance is mediated by β-lactamases, which are the most common mechanism of β-lactam resistance. Inactivation of rifampin commonly occurs through glycosylation, phosphorylation, or adenosine diphosphate (ADP) ribosylation, and resistance to macrolides and lincosamides can also occur due to enzymatic inactivation of the drug or modification.

## Prevention of Cellular Uptake or Efflux

Microbes may develop resistance mechanisms that involve inhibiting the accumulation of an antimicrobial drug, which then prevents the drug from reaching its cellular target. This strategy is common among gram-negative pathogens and can involve changes in outer membrane lipid composition, porin channel selectivity, and/or porin channel concentrations. For example, a common mechanism of carbapenem resistance among *Pseudomonas aeruginosa* is to decrease the amount of its OprD porin, which is the primary portal of entry for carbapenems through the outer membrane of this pathogen. Additionally, many gram-positive and gram-negative pathogenic bacteria produce efflux pumps that actively transport an antimicrobial drug out of the cell and prevent the accumulation of drug to a level that would be antibacterial. For example, resistance to β-lactams, tetracyclines, and fluoroquinolones commonly occurs through active efflux out of the cell, and it is rather common for a single efflux pump to have the ability to translocate multiple types of antimicrobials.

## Target Modification

Because antimicrobial drugs have very specific targets, structural changes to those targets can prevent drug binding, rendering the drug ineffective. Through spontaneous mutations in the genes encoding antibacterial drug targets, bacteria have an evolutionary advantage that allows them to develop resistance to drugs. This mechanism of resistance development is quite common. Genetic changes impacting the active site of penicillin-binding proteins (PBPs) can inhibit the binding of β-lactam drugs and provide resistance to multiple drugs within this class. This mechanism is very common among strains of *Streptococcus pneumoniae*, which alter their own PBPs through genetic mechanisms. In contrast, strains of *Staphylococcus aureus* develop resistance to methicillin (MRSA) through the acquisition of a new low-affinity PBP, rather than structurally alter their existing PBPs. Not only does this new low-affinity PBP provide resistance to methicillin but it provides resistance to virtually all β-lactam drugs, with the exception of the newer fifth-generation cephalosporins designed specifically to kill MRSA. Other examples of this resistance strategy include alterations in

- ribosome subunits, providing resistance to macrolides, tetracyclines, and aminoglycosides;
- lipopolysaccharide (LPS) structure, providing resistance to polymyxins;
- RNA polymerase, providing resistance to rifampin;
- DNA gyrase, providing resistance to fluoroquinolones;
- metabolic enzymes, providing resistance to sulfa drugs, sulfones, and trimethoprim; and
- peptidoglycan subunit peptide chains, providing resistance to glycopeptides.

## Target Overproduction or Enzymatic Bypass

When an antimicrobial drug functions as an antimetabolite, targeting a specific enzyme to inhibit its activity, there are additional ways that microbial resistance may occur. First, the microbe may overproduce the target enzyme such that there is a sufficient amount of antimicrobial-free enzyme to carry out the proper enzymatic reaction. Second, the bacterial cell may develop a bypass that circumvents the need for the functional target enzyme. Both of these strategies have been found as mechanisms of sulfonamide resistance. Vancomycin resistance among *S. aureus* has been shown to involve the decreased cross-linkage of peptide chains in the bacterial cell wall, which provides an increase in targets for vancomycin to bind to in the outer cell wall. Increased binding of vancomycin in the outer cell wall provides a blockage that prevents free drug molecules from penetrating to where they can block new cell wall synthesis.

## Target Mimicry

A recently discovered mechanism of resistance called target mimicry involves the production of proteins that bind and sequester drugs, preventing the drugs from binding to their target. For example, *Mycobacterium tuberculosis* produces a protein with regular pentapeptide repeats that appears to mimic the structure of DNA. This protein binds fluoroquinolones, sequestering them and keeping them from binding to DNA, providing *M. tuberculosis* resistance to fluoroquinolones. Proteins that mimic the A-site of

the bacterial ribosome have been found to contribute to aminoglycoside resistance as well.[1]

**Exercise 9.5.1**

List several mechanisms for drug resistance.

## Multidrug-Resistant Microbes and Cross Resistance

From a clinical perspective, our greatest concerns are multidrug-resistant microbes (MDRs) and cross resistance. MDRs are colloquially known as "superbugs" and carry one or more resistance mechanism(s), making them resistant to multiple antimicrobials. In cross-resistance, a single resistance mechanism confers resistance to multiple antimicrobial drugs. For example, having an efflux pump that can export multiple antimicrobial drugs is a common way for microbes to be resistant to multiple drugs by using a single resistance mechanism. In recent years, several clinically important superbugs have emerged, and the CDC reports that superbugs are responsible for more than 2 million infections in the US annually, resulting in at least 23,000 fatalities.[2] Several of the superbugs discussed in the following sections have been dubbed the ESKAPE pathogens. This acronym refers to the names of the pathogens (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacter* spp.) but it is also fitting in that these pathogens are able to "escape" many conventional forms of antimicrobial therapy. As such, infections by ESKAPE pathogens can be difficult to treat and they cause a large number of nosocomial infections.

## Methicillin-Resistant *Staphylococcus aureus* (MRSA)

Methicillin, a semisynthetic penicillin, was designed to resist inactivation by β-lactamases. Unfortunately, soon after the introduction of methicillin to clinical practice, methicillin-resistant strains of *S. aureus* appeared and started to spread. The mechanism of resistance, acquisition of a new low-affinity PBP, provided *S. aureus* with resistance to all available β-lactams. Strains of methicillin-resistant *S. aureus* (MRSA) are widespread opportunistic pathogens and a particular concern for skin and other wound infections, but may also cause pneumonia and septicemia. Although originally a problem in health-care settings (hospital-acquired MRSA [HA-MRSA]), MRSA infections are now also acquired through contact with contaminated members of the general public, called community-associated MRSA (CA-MRSA). Approximately one-third of the population carries *S. aureus* as a member of their normal nasal microbiota without illness, and about 6% of these strains are methicillin resistant.[3,4]

### Clavulanic Acid: Penicillin's Little Helper

With the introduction of penicillin in the early 1940s, and its subsequent mass production, society began to think of antibiotics as miracle cures for a wide range of infectious diseases. Unfortunately, as early as 1945, penicillin resistance was first documented and started to spread. Greater than 90% of current *S. aureus* clinical isolates are resistant to penicillin.[5]

Although developing new antimicrobial drugs is one solution to this problem, scientists have explored new approaches, including the development of compounds that inactivate resistance mechanisms. The development of clavulanic acid represents an early example of this strategy. Clavulanic acid is a molecule produced by the bacterium *Streptococcus clavuligerus*. It contains a β-lactam ring, making it structurally similar to penicillin and other β-lactams, but shows no clinical effectiveness when administered on its own. Instead, clavulanic acid binds irreversibly within the active site of β-lactamases and prevents them from inactivating a coadministered penicillin.

Clavulanic acid was first developed in the 1970s and was mass marketed in combination with amoxicillin beginning in the 1980s under the brand name Augmentin. As is typically the case, resistance to the amoxicillin-clavulanic acid combination soon appeared. Resistance most commonly results from bacteria increasing production of their β-lactamase and overwhelming the inhibitory effects of clavulanic acid, mutating their β-lactamase so it is no longer inhibited by clavulanic acid, or from acquiring a new β-lactamase that is not inhibited by clavulanic acid. Despite increasing resistance concerns, clavulanic acid and related β-lactamase inhibitors (sulbactam and tazobactam) represent an important new strategy: the development of compounds that directly inhibit antimicrobial resistance-conferring enzymes.

## Vancomycin-Resistant Enterococci and *Staphylococcus aureus*

Vancomycin is only effective against gram-positive organisms, and it is used to treat wound infections, septic infections, endocarditis, and meningitis that are caused by pathogens resistant to other antibiotics. It is considered one of the last lines of defense against such resistant infections, including MRSA. With the rise of antibiotic resistance in the 1970s and 1980s, vancomycin use increased, and it is not surprising that we saw the emergence and spread of vancomycin-resistant enterococci (VRE), vancomycin-resistant *S. aureus* (VRSA), and vancomycin-intermediate *S. aureus*(VISA). The mechanism of vancomycin resistance among enterococci is target modification involving a structural change to the peptide component of the peptidoglycan subunits, preventing vancomycin from binding. These strains are typically spread among patients in clinical settings by contact with health-care workers and contaminated surfaces and medical equipment.

VISA and VRSA strains differ from each other in the mechanism of resistance and the degree of resistance each mechanism confers. VISA strains exhibit intermediate resistance, with a minimum inhibitory concentration (MIC) of 4–8 μg/mL, and the mechanism involves an increase in vancomycin targets. VISA strains decrease the crosslinking of peptide chains in the cell wall, providing an increase in vancomycin targets that trap vancomycin in the outer cell wall. In contrast, VRSA strains acquire vancomycin resistance through horizontal transfer of resistance genes from VRE, an opportunity provided in individuals coinfected with both VRE and MRSA. VRSA exhibit a higher level of resistance, with MICs of 16 μg/mL or higher.[6] In the case of all three types of vancomycin-resistant bacteria, rapid clinical identification is necessary so proper procedures to limit spread can be implemented. The oxazolidinones like linezolid are useful for the treatment of these vancomycin-resistant, opportunistic pathogens, as well as MRSA.

## Extended-Spectrum β-Lactamase–Producing Gram-Negative Pathogens

Gram-negative pathogens that produce extended-spectrum β-lactamases (ESBLs) show resistance well beyond just penicillins. The spectrum of β-lactams inactivated by ESBLs provides for resistance to all penicillins, cephalosporins, monobactams, and the β-lactamase-inhibitor combinations, but not the carbapenems. An even greater concern is that the genes encoding for ESBLs are usually found on mobile plasmids that also contain genes for resistance to other drug classes (e.g., fluoroquinolones, aminoglycosides, tetracyclines), and may be readily spread to other bacteria by horizontal gene transfer. These multidrug-resistant bacteria are members of the intestinal microbiota of some individuals, but they are also important causes of opportunistic infections in hospitalized patients, from whom they can be spread to other people.

## Carbapenem-Resistant Gram-Negative Bacteria

The occurrence of carbapenem-resistant Enterobacteriaceae (CRE) and carbapenem resistance among other gram-negative bacteria (e.g., *P. aeruginosa*, *Acinetobacter baumannii*, *Stenotrophomonas maltophila*) is a growing health-care concern. These pathogens develop resistance to carbapenems through a variety of mechanisms, including production of carbapenemases (broad-spectrum β-lactamases that inactivate all β-lactams, including carbapenems), active efflux of carbapenems out of the cell, and/or prevention of carbapenem entry through porin channels. Similar to concerns with ESBLs, carbapenem-resistant, gram-negative pathogens are usually resistant to multiple classes of antibacterials, and some have even developed pan-resistance (resistance to all available antibacterials). Infections with carbapenem-resistant, gram-negative pathogens commonly occur in health-care settings through interaction with contaminated individuals or medical devices, or as a result of surgery.

## Multidrug-Resistant Mycobacterium tuberculosis

The emergence of multidrug-resistant *Mycobacterium tuberculosis* (MDR-TB) and extensively drug-resistant*Mycobacterium tuberculosis* (XDR-TB) is also of significant global concern. MDR-TB strains are resistant to both rifampin and isoniazid, the drug combination typically prescribed for treatment of tuberculosis. XDR-TB strains are additionally resistant to any fluoroquinolone and at least one of three other drugs (amikacin, kanamycin, or capreomycin) used as a second line of treatment, leaving these patients very few treatment options. Both types of pathogens are particularly problematic in immunocompromised persons, including those suffering from HIV infection. The development of resistance in these strains often results from the incorrect use of antimicrobials for tuberculosistreatment, selecting for resistance.

### Exercise 9.5.2

How does drug resistance lead to superbugs?

### Link to Learning

To learn more about the top 18 drug-resistant threats to the US, visit the CDC's website.

### Factory Farming and Drug Resistance

Although animal husbandry has long been a major part of agriculture in America, the rise of concentrated animal feeding operations (CAFOs) since the 1950s has brought about some new environmental issues, including the contamination of water and air with biological waste, and ethical issues regarding animal rights also are associated with growing animals in this way. Additionally, the increase in CAFOs involves the extensive use of antimicrobial drugs in raising livestock. Antimicrobials are used to prevent the development of infectious disease in the close quarters of CAFOs; however, the majority of antimicrobials used in factory farming are for the promotion of growth—in other words, to grow larger animals.

The mechanism underlying this enhanced growth remains unclear. These antibiotics may not necessarily be the same as those used clinically for humans, but they are structurally related to drugs used for humans. As a result, use of antimicrobial drugs in animals can select for antimicrobial resistance, with these resistant bacteria becoming cross-resistant to drugs typically used in humans. For example, tylosin use in animals appears to select for bacteria also cross-resistant to other macrolides, including erythromycin, commonly used in humans.

Concentrations of the drug-resistant bacterial strains generated by CAFOs become increased in water and soil surrounding these farms. If not directly pathogenic in humans, these resistant bacteria may serve as a reservoir of mobile genetic elements that can then pass resistance genes to human pathogens. Fortunately, the cooking process typically inactivates any antimicrobials remaining in meat, so humans typically are not directly ingesting these drugs. Nevertheless, many people are calling for more judicious use of these drugs, perhaps charging farmers user fees to reduce indiscriminate use. In fact, in 2012, the FDA published guidelines for farmers who voluntarily phase out the use of antimicrobial drugs except under veterinary supervision and when necessary to ensure animal health. Although following the guidelines is voluntary at this time, the FDA does recommend what it calls "judicious" use of antimicrobial drugs in food-producing animals in an effort to decrease antimicrobial resistance.

### Clinical Focus: Part 3

Unfortunately, Marisa's urinary tract infection did not resolve with ciprofloxacin treatment. Laboratory testing showed that her infection was caused by a strain of *Klebsiella pneumoniae* with significant antimicrobial resistance. The resistance profile of this *K. pneumoniae* included resistance to the carbapenem class of antibacterials, a group of β-lactams that is typically reserved for the treatment of highly resistant bacteria. *K. pneumoniae* is an opportunistic, capsulated, gram-negative rod that may be a member of the normal microbiota of the intestinal tract, but may also cause a number of diseases, including pneumonia and UTIs.

Specific laboratory tests looking for carbapenemase production were performed on Marisa's samples and came back positive. Based upon this result, in combination with her health history, production of a carbapenemase known as the New Delhi Metallo-β-lactamase (NDM) was suspected. Although the origin of the NDM carbapenemase is not completely known, many patients infected with NDM-containing strains have travel histories involving hospitalizations in India or surrounding countries.

#### Exercise 9.5.1

How would doctors determine which types of antimicrobial drugs should be administered?

## Key Concepts and Summary

- **Antimicrobial resistance** is on the rise and is the result of selection of drug-resistant strains in clinical environments, the overuse and misuse of antibacterials, the use of subtherapeutic doses of antibacterial drugs, and poor patient compliance with antibacterial drug therapies.
- Drug resistance genes are often carried on plasmids or in transposons that can undergo vertical transfer easily and between microbes through horizontal gene transfer.
- Common modes of antimicrobial drug resistance include drug modification or inactivation, prevention of cellular uptake or efflux, target modification, target overproduction or enzymatic bypass, and target mimicry.
- Problematic microbial strains showing extensive antimicrobial resistance are emerging; many of these strains can reside as members of the normal microbiota in individuals but also can cause opportunistic infection. The transmission of many of these highly resistant microbial strains often occurs in clinical settings, but can also be community-acquired.

## Footnotes

1. 1 D.H. Fong, A.M. Berghuis. “Substrate Promiscuity of an Aminoglycoside Antibiotic Resistance Enzyme Via Target Mimicry.” *EMBO Journal* 21 no. 10 (2002):2323–2331.
2. 2 Centers for Disease Control and Prevention. “Antibiotic/Antimicrobial Resistance.” http://www.cdc.gov/drugresistance/index.html. Accessed June 2, 2016.
3. 3 A.S. Kalokhe et al. “Multidrug-Resistant Tuberculosis Drug Susceptibility and Molecular Diagnostic Testing: A Review of the Literature. *American Journal of the Medical Sciences* 345 no. 2 (2013):143–148.
4. 4 Centers for Disease Control and Prevention. “Methicillin-Resistant *Staphylococcus aureus* (MRSA): General Information About MRSA in the Community.” http://www.cdc.gov/mrsa/community/index.html. Accessed June 2, 2016
5. 5 F.D. Lowy. “Antimicrobial Resistance: The Example of *Staphylococcus aureus*.” *Journal of Clinical Investigation* 111 no. 9 (2003):1265–1273.
6. 6 Centers for Disease Control and Prevention. “Healthcare-Associated Infections (HIA): General Information about VISA/VRSA.” www.cdc.gov/HAI/organisms/vis...visa_vrsa.html. Accessed June 2, 2016.

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# 9.6: Testing the Effectiveness of Antimicrobials

## Learning Objectives

- Describe how the Kirby-Bauer disk diffusion test determines the susceptibility of a microbe to an antibacterial drug.
- Explain the significance of the minimal inhibitory concentration and the minimal bactericidal concentration relative to the effectiveness of an antimicrobial drug.

Testing the effectiveness of antimicrobial drugs against specific organisms is important in identifying their spectrum of activity and the therapeutic dosage. This type of test, generally described as antimicrobial susceptibility testing (AST), is commonly performed in a clinical laboratory. In this section, we will discuss common methods of testing the effectiveness of antimicrobials.

## The Kirby-Bauer Disk Diffusion Test

The Kirby-Bauer disk diffusion test has long been used as a starting point for determining the susceptibility of specific microbes to various antimicrobial drugs. The Kirby-Bauer assay starts with a Mueller-Hinton agar plate on which a confluent lawn is inoculated with a patient's isolated bacterial pathogen. Filter paper disks impregnated with known amounts of antibacterial drugs to be tested are then placed on the agar plate. As the bacterial inoculum grows, antibiotic diffuses from the circular disk into the agar and interacts with the growing bacteria. Antibacterial activity is observed as a clear circular zone of inhibition around the drug-impregnated disk, similar to the disk-diffusion assay. The diameter of the zone of inhibition, measured in millimeters and compared to a standardized chart, determines the susceptibility or resistance of the bacterial pathogen to the drug.

There are multiple factors that determine the size of a zone of inhibition in this assay, including drug solubility, rate of drug diffusion through agar, the thickness of the agar medium, and the drug concentration impregnated into the disk. Due to a lack of standardization of these factors, interpretation of the Kirby-Bauer disk diffusion assay provides only limited information on susceptibility and resistance to the drugs tested. The assay cannot distinguish between bacteriostatic and bactericidal activities, and differences in zone sizes cannot be used to compare drug potencies or efficacies. Comparison of zone sizes to a standardized chart will only provide information on the antibacterials to which a bacterial pathogen is susceptible or resistant.

### Exercise 9.6.1

How does one use the information from a Kirby-Bauer assay to predict the therapeutic effectiveness of an antimicrobial drug in a patient?

### Antibiograms: Taking Some of the Guesswork Out of Prescriptions

Unfortunately, infectious diseases don't take a time-out for lab work. As a result, physicians rarely have the luxury of conducting susceptibility testing before they write a prescription. Instead, they rely primarily on the empirical evidence (i.e., the signs and symptoms of disease) and their professional experience to make an educated guess as to the diagnosis, causative agent(s), and drug most likely to be effective. This approach allows treatment to begin sooner so the patient does not have to wait for lab test results. In many cases, the prescription is effective; however, in an age of increased antimicrobial resistance, it is becoming increasingly more difficult to select the most appropriate empiric therapy. Selecting an inappropriate empiric therapy not only puts the patient at risk but may promote greater resistance to the drug prescribed.

Recently, studies have shown that antibiograms are useful tools in the decision-making process of selecting appropriate empiric therapy. An antibiogram is a compilation of local antibiotic susceptibility data broken down by bacterial pathogen. In a November 2014 study published in the journal *Infection Control and Hospital Epidemiology*, researchers determined that 85% of the prescriptions ordered in skilled nursing facilities were decided upon empirically, but only 35% of those prescriptions were deemed appropriate when compared with the eventual pathogen identification and susceptibility profile obtained from the clinical laboratory. However, in one nursing facility where use of antibiograms was implemented to direct selection of empiric therapy, appropriateness of empiric therapy increased from 32% before antibiogram implementation to

45% after implementation of antibiograms.[1] Although these data are preliminary, they do suggest that health-care facilities can reduce the number of inappropriate prescriptions by using antibiograms to select empiric therapy, thus benefiting patients and minimizing opportunities for antimicrobial resistance to develop.

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Visit this website to view an interactive antibiogram provided by Stanford University.

## Dilution Tests

As discussed, the limitations of the Kirby-Bauer disk diffusion test do not allow for a direct comparison of antibacterial potencies to guide selection of the best therapeutic choice. However, antibacterial dilution tests can be used to determine a particular drug's minimal inhibitory concentration (MIC), the lowest concentration of drug that inhibits visible bacterial growth, and minimal bactericidal concentration (MBC), the lowest drug concentration that kills ≥99.9% of the starting inoculum. Determining these concentrations helps identify the correct drug for a particular pathogen. For the macrobroth dilution assay, a dilution series of the drug in broth is made in test tubes and the same number of cells of a test bacterial strain is added to each tube (Figure 9.6.1). The MIC is determined by examining the tubes to find the lowest drug concentration that inhibits visible growth; this is observed as turbidity (cloudiness) in the broth. Tubes with no visible growth are then inoculated onto agar media without antibiotic to determine the MBC. Generally, serum levels of an antibacterial should be at least three to five times above the MIC for treatment of an infection.

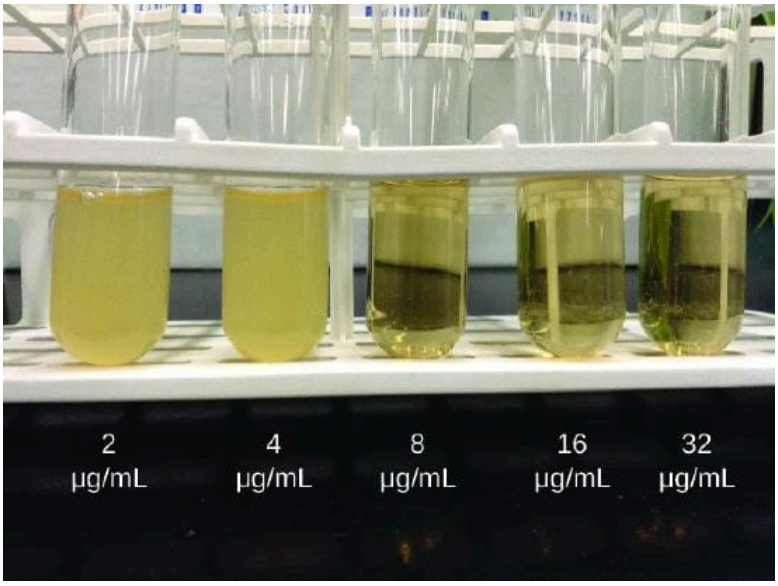



Figure 9.6.1: In a dilution test, the lowest dilution that inhibits turbidity (cloudiness) is the MIC. In this example, the MIC is 8 µg/mL. Broth from samples without turbidity can be inoculated onto plates lacking the antimicrobial drug. The lowest dilution that kills ≥99.9% of the starting inoculum is observed on the plates is the MBC. (credit: modification of work by Suzanne Wakim)

The MIC assay can also be performed using 96-well microdilution trays, which allow for the use of small volumes and automated dispensing devices, as well as the testing of multiple antimicrobials and/or microorganisms in one tray (Figure 9.6.2). MICs are interpreted as the lowest concentration that inhibits visible growth, the same as for the macrobroth dilution in test tubes. Growth may also be interpreted visually or by using a spectrophotometer or similar device to detect turbidity or a color change if an appropriate biochemical substrate that changes color in the presence of bacterial growth is also included in each well.

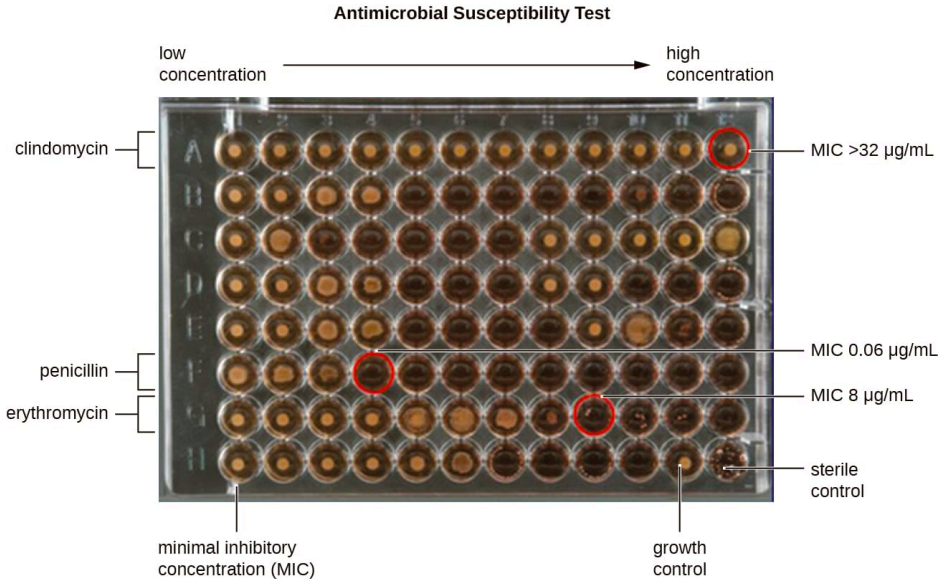



Figure 9.6.2: A microdilution tray can also be used to determine MICs of multiple antimicrobial drugs in a single assay. In this example, the drug concentrations increase from left to right and the rows with clindamycin, penicillin, and erythromycin have been indicated to the left of the plate. For penicillin and erythromycin, the lowest concentrations that inhibited visible growth are indicated by red circles and were 0.06 µg/mL for penicillin and 8 µg/mL for erythromycin. For clindamycin, visible bacterial growth was observed at every concentration up to 32 µg/mL and the MIC is interpreted as >32 µg/mL. (credit: modification of work by Centers for Disease Control and Prevention)

The Etest is an alternative method used to determine MIC, and is a combination of the Kirby-Bauer disk diffusion testand dilution methods. Similar to the Kirby-Bauer assay, a confluent lawn of a bacterial isolate is inoculated onto the surface of an agar plate. Rather than using circular disks impregnated with one concentration of drug, however, commercially available plastic strips that contain a gradient of an antibacterial are placed on the surface of the inoculated agar plate (Figure 9.6.3). As the bacterial inoculum grows, antibiotic diffuses from the plastic strips into the agar and interacts with the bacterial cells. Because the rate of drug diffusion is directly related to concentration, an elliptical zone of inhibition is observed with the Etest drug gradient, rather than a circular zone of inhibition observed with the Kirby-Bauer assay. To interpret the results, the intersection of the elliptical zone with the gradient on the drug-containing strip indicates the MIC. Because multiple strips containing different antimicrobials can be placed on the same plate, the MIC of multiple antimicrobials can be determined concurrently and directly compared. However, unlike the macrobroth and microbroth dilution methods, the MBC cannot be determined with the Etest.

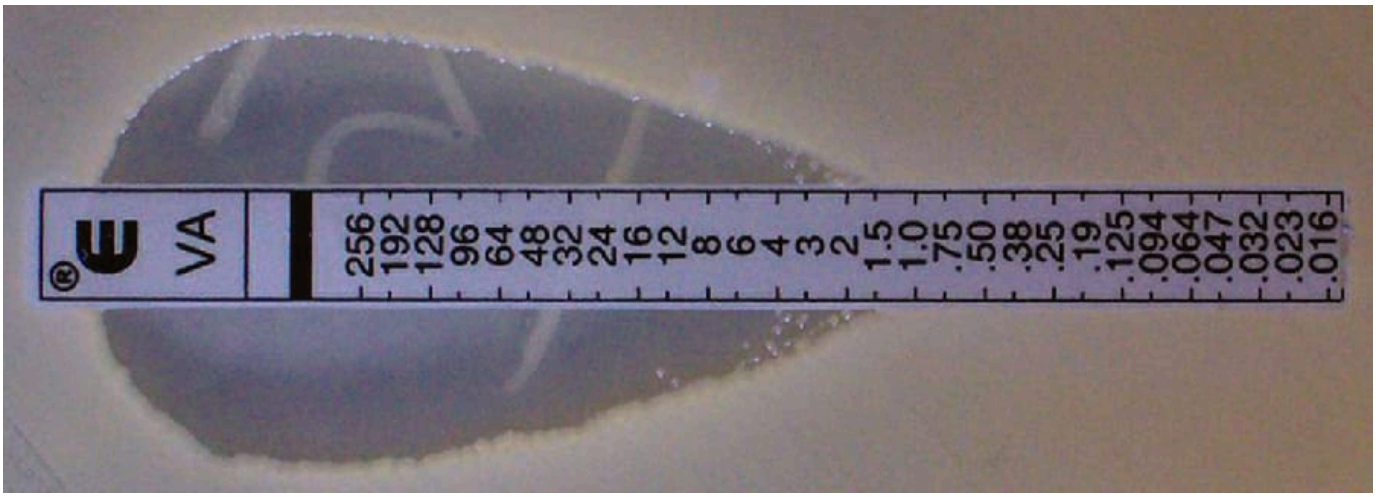



Figure 9.6.3: The Etest can be used to determine the MIC of an antibiotic. In this Etest, vancomycin is shown to have a MIC of 1.5 µg/mL against *Staphylococcus aureus*.

## Exercise 9.6.2

Compare and contrast MIC and MBC.

## Clinical Focus: Resolution

Marisa's UTI was likely caused by the catheterizations she had in Vietnam. Most bacteria that cause UTIs are members of the normal gut microbiota, but they can cause infections when introduced to the urinary tract, as might have occurred when the catheter was inserted. Alternatively, if the catheter itself was not sterile, bacteria on its surface could have been introduced into Marisa's body. The antimicrobial therapy Marisa received in Cambodia may also have been a complicating factor because it may have selected for antimicrobial-resistant strains already present in her body. These bacteria would have already contained genes for antimicrobial resistance, either acquired by spontaneous mutation or through horizontal gene transfer, and, therefore, had the best evolutionary advantage for adaptation and growth in the presence of the antimicrobial therapy. As a result, one of these resistant strains may have been subsequently introduced into her urinary tract.

Laboratory testing at the CDC confirmed that the strain of *Klebsiella pneumoniae* from Marisa's urine sample was positive for the presence of NDM, a very active carbapenemasethat is beginning to emerge as a new problem in antimicrobial resistance. While NDM-positive strains are resistant to a wide range of antimicrobials, they have shown susceptibility to tigecycline (structurally related to tetracycline) and the polymyxins B and E (colistin).

To prevent her infection from spreading, Marisa was isolated from the other patients in a separate room. All hospital staff interacting with her were advised to follow strict protocols to prevent surface and equipment contamination. This would include especially stringent hand hygiene practices and careful disinfection of all items coming into contact with her.

Marisa's infection finally responded to tigecycline and eventually cleared. She was discharged a few weeks after admission, and a follow-up stool sample showed her stool to be free of NDM-containing *K. pneumoniae*, meaning that she was no longer harboring the highly resistant bacterium.

## Key Concepts and Summary

- The **Kirby-Bauer disk diffusion** test helps determine the susceptibility of a microorganism to various antimicrobial drugs. However, the **zones of inhibition** measured must be correlated to known standards to determine susceptibility and resistance, and do not provide information on bactericidal versus bacteriostatic activity, or allow for direct comparison of drug potencies.
- Antibiograms are useful for monitoring local trends in antimicrobial resistance/susceptibility and for directing appropriate selection of empiric antibacterial therapy.
- There are several laboratory methods available for determining the **minimum inhibitory concentration (MIC)** of an antimicrobial drug against a specific microbe. The **minimal bactericidal concentration (MBC)** can also be determined, typically as a follow-up experiment to MIC determination using the tube dilution method.

## Footnotes

1. 1 J.P. Furuno et al. "Using Antibiograms to Improve Antibiotic Prescribing in Skilled Nursing Facilities." *Infection Control and Hospital Epidemiology* 35 no. Suppl S3 (2014):S56–61.

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# 9.7: Current Strategies for Antimicrobial Discovery

## Learning Objectives

- Describe the methods and strategies used for discovery of new antimicrobial agents.

With the continued evolution and spread of antimicrobial resistance, and now the identification of pan-resistant bacterial pathogens, the search for new antimicrobials is essential for preventing the postantibiotic era. Although development of more effective semisynthetic derivatives is one strategy, resistance to them develops rapidly because bacterial pathogens are already resistant to earlier-generation drugs in the family and can easily mutate and develop resistance to the new semisynthetic drugs. Today, scientists continue to hunt for new antimicrobial compounds and explore new avenues of antimicrobial discovery and synthesis. They check large numbers of soils and microbial products for antimicrobial activity by using high-throughput screening methods, which use automation to test large numbers of samples simultaneously. The recent development of the iChip[1] allows researchers to investigate the antimicrobial-producing capabilities of soil microbes that are difficult to grow by standard cultivation techniques in the laboratory. Rather than grow the microbes in the laboratory, they are grown in situ—right in the soil. Use of the iChip has resulted in the discovery of teixobactin, a novel antimicrobial from Mount Ararat, Turkey. Teixobactin targets two distinct steps in gram-positive cell wall synthesis and for which antimicrobial resistance appears not yet to have evolved.

Although soils have been widely examined, other environmental niches have not been tested as fully. Since 70% of the earth is covered with water, marine environments could be mined more fully for the presence of antimicrobial-producing microbes. In addition, researchers are using combinatorial chemistry, a method for making a very large number of related compounds from simple precursors, and testing them for antimicrobial activity. An additional strategy that needs to be explored further is the development of compounds that inhibit resistance mechanisms and restore the activity of older drugs, such as the strategy described earlier for β-lactamase inhibitors like clavulanic acid. Finally, developing inhibitors of virulence factor production and function could be a very important avenue. Although this strategy would not be directly antibacterial, drugs that slow the progression of an infection could provide an advantage for the immune system and could be used successfully in combination with antimicrobial drugs.

## Exercise 9.7.1

What are new sources and strategies for developing drugs to fight infectious diseases?

## The (Free?) Market for New Antimicrobials

There used to be plenty of antimicrobial drugs on the market to treat infectious diseases. However, the spread of antimicrobial resistance has created a need for new antibiotics to replace those that are no longer as effective as they once were. Unfortunately, pharmaceutical companies are not particularly motivated to fill this need. As of 2009, all but five pharmaceutical companies had moved away from antimicrobial drug development.[2] As a result, the number of FDA approvals of new antimicrobials has fallen drastically in recent decades (Figure 9.7.1).

Given that demand usually encourages supply, one might expect pharmaceutical companies to be rushing to get back in the business of developing new antibiotics. But developing new drugs is a lengthy process and requires large investments in research and development. Pharmaceutical companies can typically get a higher return on their investment by developing products for chronic, nonmicrobial diseases like diabetes; such drugs must be taken for life, and therefore generate more long-term revenue than an antibiotic that does its job in a week or two. But what will happen when drugs like vancomycin, a superantimicrobial reserved for use as a last resort, begin to lose their effectiveness against ever more drug-resistant superbugs? Will drug companies wait until all antibiotics have become useless before beginning to look for new ones?

Recently, it has been suggested that large pharmaceutical companies should be given financial incentives to pursue such research. In September 2014, the White House released an executive order entitled “Combating Antibiotic Resistant Bacteria,” calling upon various government agencies and the private sector to work together to “accelerate basic and applied

research and development for new antimicrobials, other therapeutics, and vaccines."[3] As a result, as of March 2015, President Obama's proposed fiscal year 2016 budget doubled the amount of federal funding to $1.2 billion for "combating and preventing antibiotic resistance," which includes money for antimicrobial research and development.[4] Similar suggestions have also been made on a global scale. In December 2014, a report chaired by former Goldman Sachs economist Jim O'Neill was published in *The Review on Antimicrobial Resistance*.[5]

These developments reflect the growing belief that for-profit pharmaceutical companies must be subsidized to encourage development of new antimicrobials. But some ask whether pharmaceutical development should be motivated by profit at all. Given that millions of lives may hang in the balance, some might argue that drug companies have an ethical obligation to devote their research and development efforts to high-utility drugs, as opposed to highly profitable ones. Yet this obligation conflicts with the fundamental goals of a for-profit company. Are government subsidies enough to ensure that drug companies make the public interest a priority, or should government agencies assume responsibility for developing critical drugs that may have little or no return on investment?

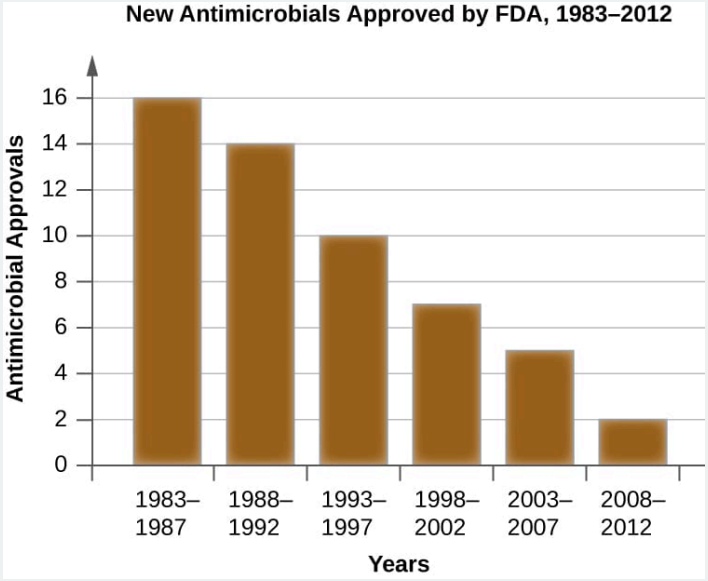



Figure 9.7.1: In recent decades, approvals of new antimicrobials by the FDA have steadily fallen. In the five-year period from 1983–1987, 16 new antimicrobial drugs were approved, compared to just two from 2008–2012.

### Link to Learning

To further examine the scope of the problem, view this video.

To learn more about the history of antimicrobial drug discovery, visit Michigan State University's Antimicrobial Resistance Learning Site.

## Key Concepts and Summary

- Current research into the development of antimicrobial drugs involves the use of high-throughput screening and combinatorial chemistry technologies.
- New technologies are being developed to discover novel antibiotics from soil microorganisms that cannot be cultured by standard laboratory methods.
- Additional strategies include searching for antibiotics from sources other than soil, identifying new antibacterial targets, using combinatorial chemistry to develop novel drugs, developing drugs that inhibit resistance mechanisms, and developing drugs that target virulence factors and hold infections in check.

## Footnotes

1. 1 L. Losee et al. “A New Antibiotic Kills Pathogens Without Detectable Resistance.” *Nature* 517 no. 7535 (2015):455–459.
2. 2 H.W. Boucher et al. “Bad Bugs, No Drugs: No ESKAPE! An Update from the Infectious Diseases Society of America.” *Clinical Infectious Diseases* 48 no. 1 (2009):1–12.
3. 3 The White House. *National Action Plan for Combating Antibiotic-Resistant Bacteria*. Washington, DC: The White House, 2015.
4. 4 White House Office of the Press Secretary. “Fact Sheet: Obama Administration Releases National Action Plan to Combat Antibiotic-Resistant Bacteria.” March 27, 2015. https://www.whitehouse.gov/the-press...lan-combat-ant
5. 5 Review on Antimicrobial Resistance. http://amr-review.org. Accessed June 1, 2016.

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# 9.8: Review Questions

## Multiple Choice

1. A scientist discovers that a soil bacterium he has been studying produces an antimicrobial that kills gram-negative bacteria. She isolates and purifies the antimicrobial compound, then chemically converts a chemical side chain to a hydroxyl group. When she tests the antimicrobial properties of this new version, she finds that this antimicrobial drug can now also kill gram-positive bacteria. The new antimicrobial drug with broad-spectrum activity is considered to be which of the following?
   A. resistant
   B. semisynthetic
   C. synthetic
   D. natural

*Answer available at the end of this section.*

2. Which of the following antimicrobial drugs is synthetic?
   A. sulfanilamide
   B. penicillin
   C. actinomycin
   D. neomycin

*Answer available at the end of this section.*

3. Which of the following combinations would most likely contribute to the development of a superinfection?
   A. long-term use of narrow-spectrum antimicrobials
   B. long-term use of broad-spectrum antimicrobials
   C. short-term use of narrow-spectrum antimicrobials
   D. short-term use of broad-spectrum antimicrobials

*Answer available at the end of this section.*

4. Which of the following routes of administration would be appropriate and convenient for home administration of an antimicrobial to treat a systemic infection?
   A. oral
   B. intravenous
   C. topical
   D. parenteral

*Answer available at the end of this section.*

5. Which clinical situation would be appropriate for treatment with a narrow-spectrum antimicrobial drug?
   A. treatment of a polymicrobic mixed infection in the intestine
   B. prophylaxis against infection after a surgical procedure
   C. treatment of strep throat caused by culture identified *Streptococcus pyogenes*
   D. empiric therapy of pneumonia while waiting for culture results

*Answer available at the end of this section.*

6. Which of the following terms refers to the ability of an antimicrobial drug to harm the target microbe without harming the host?
   A. mode of action
   B. therapeutic level
   C. spectrum of activity
   D. selective toxicity

*Answer available at the end of this section.*

7. Which of the following is not a type of β-lactam antimicrobial?
   A. penicillins
   B. glycopeptides
   C. cephalosporins
   D. monobactams

*Answer available at the end of this section.*

8. Which of the following does not bind to the 50S ribosomal subunit?
   A. tetracyclines
   B. lincosamides
   C. macrolides
   D. chloramphenicol

*Answer available at the end of this section.*

9. Which of the following antimicrobials inhibits the activity of DNA gyrase?
   A. polymyxin B
   B. clindamycin
   C. nalidixic acid
   D. rifampin

*Answer available at the end of this section.*

10. Which of the following is not an appropriate target for antifungal drugs?
    A. ergosterol
    B. chitin
    C. cholesterol
    D. β(1→3) glucan

*Answer available at the end of this section.*

11. Which of the following drug classes specifically inhibits neuronal transmission in helminths?
    A. quinolines
    B. avermectins
    C. amantadines
    D. imidazoles

*Answer available at the end of this section.*

12. Which of the following is a nucleoside analog commonly used as a reverse transcriptase inhibitor in the treatment of HIV?
    A. acyclovir
    B. ribavirin
    C. adenine-arabinoside
    D. azidothymidine

*Answer available at the end of this section.*

13. Which of the following is an antimalarial drug that is thought to increase ROS levels in target cells?
    A. artemisinin
    B. amphotericin b
    C. praziquantel
    D. pleconaril

*Answer available at the end of this section.*

14. Which of the following resistance mechanisms describes the function of β-lactamase?
    A. efflux pump
    B. target mimicry
    C. drug inactivation
    D. target overproduction

*Answer available at the end of this section.*

15. Which of the following resistance mechanisms is commonly effective against a wide range of antimicrobials in multiple classes?
    A. efflux pump
    B. target mimicry
    C. target modification
    D. target overproduction

*Answer available at the end of this section.*

16. Which of the following resistance mechanisms is the most nonspecific to a particular class of antimicrobials?
    A. drug modification
    B. target mimicry
    C. target modification
    D. efflux pump

*Answer available at the end of this section.*

17. Which of the following types of drug-resistant bacteria do not typically persist in individuals as a member of their intestinal microbiota?
    A. MRSA
    B. VRE
    C. CRE
    D. ESBL-producing bacteria

*Answer available at the end of this section.*

18. In the Kirby-Bauer disk diffusion test, the _____ of the zone of inhibition is measured and used for interpretation.
    A. diameter
    B. microbial population
    C. circumference
    D. depth

*Answer available at the end of this section.*

19. Which of the following techniques cannot be used to determine the minimum inhibitory concentration of an antimicrobial drug against a particular microbe?
    A. Etest
    B. microbroth dilution test
    C. Kirby-Bauer disk diffusion test
    D. macrobroth dilution test

*Answer available at the end of this section.*

20. The utility of an antibiogram is that it shows antimicrobial susceptibility trends
    A. over a large geographic area.
    B. for an individual patient.
    C. in research laboratory strains.
    D. in a localized population.

*Answer available at the end of this section.*

21. Which of the following has yielded compounds with the most antimicrobial activity?
    A. water
    B. air
    C. volcanoes
    D. soil

*Answer available at the end of this section.*

## True/False

22. Narrow-spectrum antimicrobials are commonly used for prophylaxis following surgery.

*Answer available at the end of this section.*

23. β-lactamases can degrade vancomycin.

*Answer available at the end of this section.*

24. Echinocandins, known as "penicillin for fungi," target β(1→3) glucan in fungal cell walls.

*Answer available at the end of this section.*

25. If drug A produces a larger zone of inhibition than drug B on the Kirby-Bauer disk diffusion test, drug A should always be prescribed.

*Answer available at the end of this section.*

26. The rate of discovery of antimicrobial drugs has decreased significantly in recent decades.

*Answer available at the end of this section.*

## Fill in the Blank

27. The group of soil bacteria known for their ability to produce a wide variety of antimicrobials is called the _____.

*Answer available at the end of this section.*

28. The bacterium known for causing pseudomembranous colitis, a potentially deadly superinfection, is _____.

*Answer available at the end of this section.*

29. Selective toxicity antimicrobials are easier to develop against bacteria because they are _____ cells, whereas human cells are eukaryotic.

*Answer available at the end of this section.*

30. Antiviral drugs, like Tamiflu and Relenza, that are effective against the influenza virus by preventing viral escape from host cells are called _____.

*Answer available at the end of this section.*

31. *Staphylococcus aureus*, including MRSA strains, may commonly be carried as a normal member of the _____ microbiota in some people.

*Answer available at the end of this section.*

32. The method that can determine the MICs of multiple antimicrobial drugs against a microbial strain using a single agar plate is called the _____.

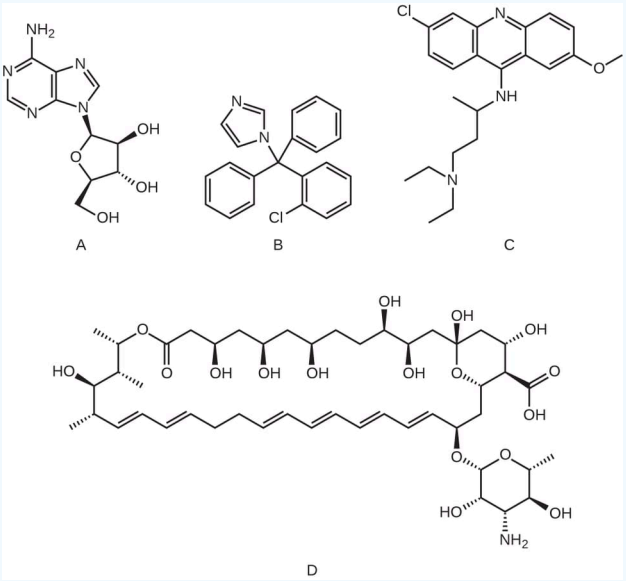
*Answer available at the end of this section.*

## Short Answer

33. Where do antimicrobials come from naturally? Why?
34. Why was Salvarsan considered to be a “magic bullet” for the treatment of syphilis?
35. When prescribing antibiotics, what aspects of the patient’s health history should the clinician ask about and why?
36. When is using a broad-spectrum antimicrobial drug warranted?
37. If human cells and bacterial cells perform transcription, how are the rifamycins specific for bacterial infections?
38. What bacterial structural target would make an antibacterial drug selective for gram-negative bacteria? Provide one example of an antimicrobial compound that targets this structure.
39. How does the biology of HIV necessitate the need to treat HIV infections with multiple drugs?
40. Niclosamide is insoluble and thus is not readily absorbed from the stomach into the bloodstream. How does the insolubility of niclosamide aid its effectiveness as a treatment for tapeworm infection?
41. Why does the length of time of antimicrobial treatment for tuberculosis contribute to the rise of resistant strains?
42. What is the difference between multidrug resistance and cross-resistance?
43. How is the information from a Kirby-Bauer disk diffusion test used for the recommendation of the clinical use of an antimicrobial drug?
44. What is the difference between MIC and MBC?

## Critical Thinking

45. In nature, why do antimicrobial-producing microbes commonly also have antimicrobial resistance genes?
46. Why are yeast infections a common type of superinfection that results from long-term use of broad-spectrum antimicrobials?
47. Too often patients will stop taking antimicrobial drugs before the prescription is finished. What are factors that cause a patient to stop too soon, and what negative impacts could this have?
48. In considering the cell structure of prokaryotes compared with that of eukaryotes, propose one possible reason for side effects in humans due to treatment of bacterial infections with protein synthesis inhibitors.
49. Which of the following molecules is an example of a nucleoside analog?



50. Why can't drugs used to treat influenza, like amantadines and neuraminidase inhibitors, be used to treat a wider variety of viral infections?
51. Can an Etest be used to find the MBC of a drug? Explain.
52. Who should be responsible for discovering and developing new antibiotics? Support your answer with reasoning.

## Answers

**Multiple Choice**
B

**Multiple Choice**
A

**Multiple Choice**
B

**Multiple Choice**
A

**Multiple Choice**
C

**Multiple Choice**
D

**Multiple Choice**
B

**Multiple Choice**
A

**Multiple Choice**
C

**Multiple Choice**
C

**Multiple Choice**
B

**Multiple Choice**
D

**Multiple Choice**
A

**Multiple Choice**
C

**Multiple Choice**
A

**Multiple Choice**
D

**Multiple Choice**
A

**Multiple Choice**
A

**Multiple Choice**
C

**Multiple Choice**
D

**Multiple Choice**
D

**True/False**
False

**True/False**
false

**True/False**
true

**True/False**

false

**True/False**

true

**Fill in the Blank**

actinomycetes

**Fill in the Blank**

*Clostridium difficile*

**Fill in the Blank**

prokaryotic

**Fill in the Blank**

neuraminidase inhibitors

**Fill in the Blank**

nasal

**Fill in the Blank**

Etest

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# 10: Antibiotics vs. Bacteria - Fighting the Resistance (Video)

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# WEEK 6

## 11: Digestive System Infections


11.1: Anatomy and Normal Microbiota of the Digestive System

11.2: Microbial Diseases of the Mouth and Oral Cavity

11.3: Bacterial Infections of the Gastrointestinal Tract

11.4: Viral Infections of the Gastrointestinal Tract

11.5: Protozoan Infections of the Gastrointestinal Tract

11.6: Helminthic Infections of the Gastrointestinal Tract

11.7: Review Questions


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# 11.1: Anatomy and Normal Microbiota of the Digestive System

## Learning Objectives

- Describe the major anatomical features of the human digestive system
- Describe the normal microbiota of various regions in the human digestive system
- Explain how microorganisms overcome the defenses of the digestive tract to cause infection or intoxication
- Describe general signs and symptoms associated with infections of the digestive system

## Clinical Focus: Part 1

After a morning of playing outside, four-year-old Carli ran inside for lunch. After taking a bite of her fried egg, she pushed it away and whined, “It’s too slimy, Mommy. I don’t want any more.” But her mother, in no mood for games, curtly replied that if she wanted to go back outside she had better finish her lunch. Reluctantly, Carli complied, trying hard not to gag as she choked down the runny egg.

That night, Carli woke up feeling nauseated. She cried for her parents and then began to vomit. Her parents tried to comfort her, but she continued to vomit all night and began to have diarrhea and run a fever. By the morning, her parents were very worried. They rushed her to the emergency room.

### Exercise 11.1.1

What could have caused Carli’s signs and symptoms?

The human digestive system, or the gastrointestinal (GI) tract, begins with the mouth and ends with the anus. The parts of the mouth include the teeth, the gums, the tongue, the oral vestibule (the space between the gums, lips, and teeth), and the oral cavity proper (the space behind the teeth and gums). Other parts of the GI tract are the pharynx, esophagus, stomach, small intestine, large intestine, rectum, and anus (Figure 11.1.1). Accessory digestive organs include the salivary glands, liver, gallbladder, spleen, and pancreas.

The digestive system contains normal microbiota, including archaea, bacteria, fungi, protists, and even viruses. Because this microbiota is important for normal functioning of the digestive system, alterations to the microbiota by antibiotics or diet can be harmful. Additionally, the introduction of pathogens to the GI tract can cause infections and diseases. In this section, we will review the microbiota found in a healthy digestive tract and the general signs and symptoms associated with oral and GI infections.

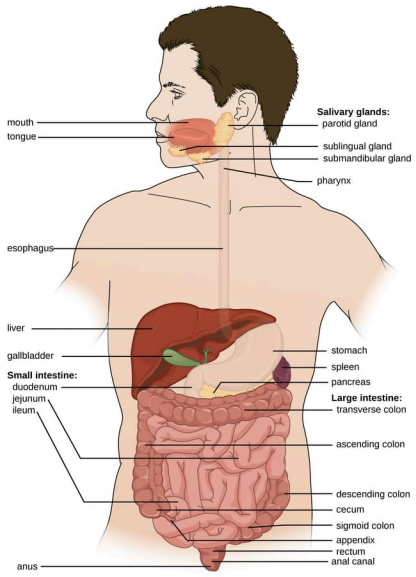



Figure 11.1.1: The digestive system, or the gastrointestinal tract, includes all of the organs associated with the digestion of food.

## Anatomy and Normal Microbiota of the Oral Cavity

Food enters the digestive tract through the mouth, where mechanical digestion (by chewing) and chemical digestion (by enzymes in saliva) begin. Within the mouth are the tongue, teeth, and salivary glands, including the parotid, sublingual, and submandibular glands (Figure 11.1.2). The salivary glands produce saliva, which lubricates food and contains digestive enzymes.

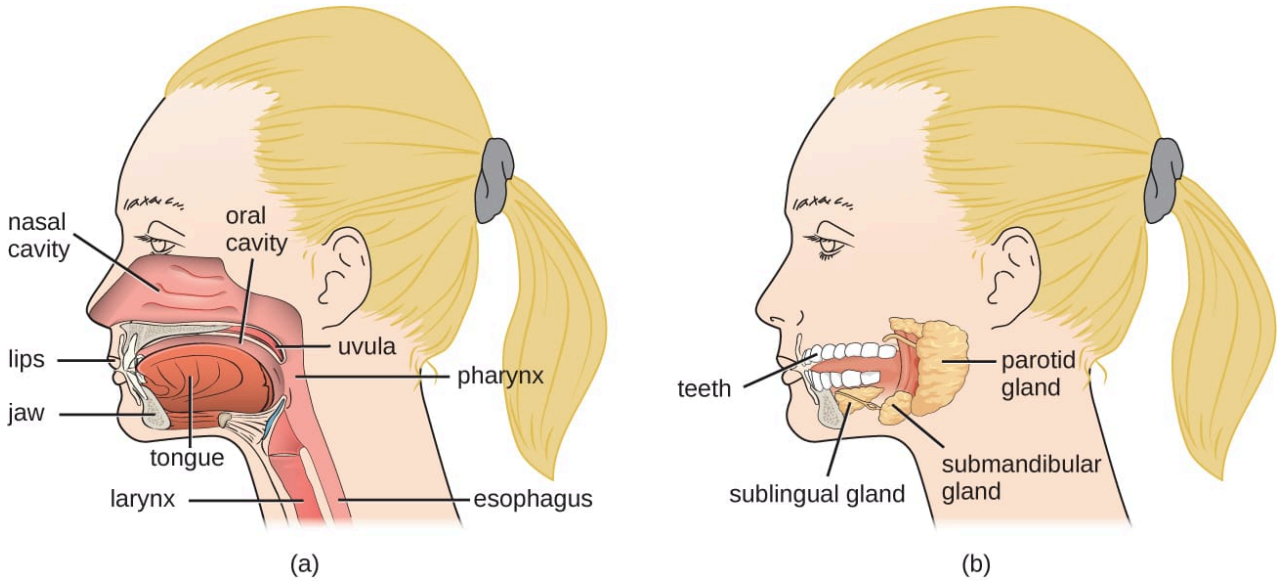



Figure 11.1.2: (a) When food enters the mouth, digestion begins. (b) Salivary glands are accessory digestive organs. (credit: modification of work by National Cancer Institute)

The structure of a tooth (Figure 11.1.3) begins with the visible outer surface, called the crown, which has to be extremely hard to withstand the force of biting and chewing. The crown is covered with enamel, which is the hardest material in the body. Underneath the crown, a layer of relatively hard dentin extends into the root of the tooth around the innermost pulp cavity, which includes the pulp chamber at the top of the tooth and pulp canal, or root canal, located in the root. The pulp that fills the pulp cavity is rich in blood vessels, lymphatic vessels, connective tissue, and nerves. The root of the tooth and some of the crown are covered with cementum, which works with the periodontal ligament to anchor the tooth in place in the jaw bone. The soft tissues surrounding the teeth and bones are called gums, or gingiva. The gingival space or gingival crevice is located between the gums and teeth.

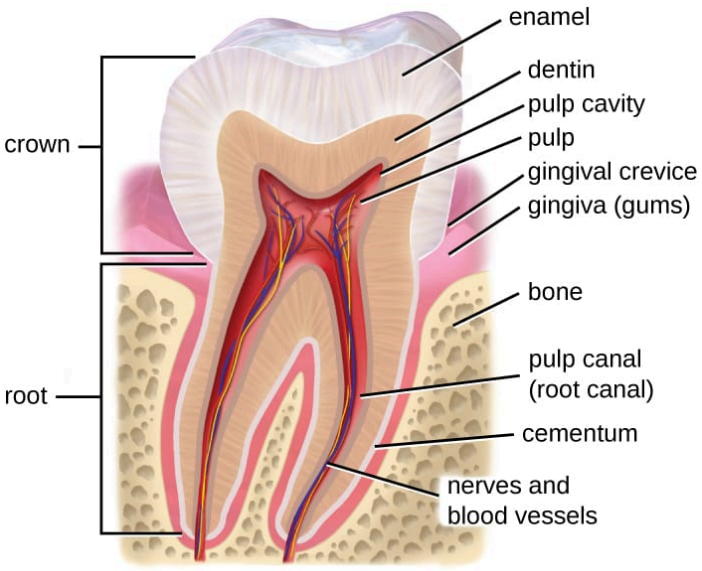



Figure 11.1.3: The tooth has a visible crown with an outer layer of enamel, a layer of dentin, and an inner pulp. The root, hidden by the gums, contains the pulp canal (root canal). (credit: modification of work by Bruce Blaus)

Microbes such as bacteria and archaea are abundant in the mouth and coat all of the surfaces of the oral cavity. However, different structures, such as the teeth or cheeks, host unique communities of both aerobic and anaerobic microbes. Some factors appear to work against making the mouth hospitable to certain microbes. For example, chewing allows microbes to mix better with saliva so they can be swallowed or spit out more easily. Saliva also contains enzymes, including lysozyme, which can damage microbial cells. Recall that lysozyme is part of the first line of defense in the innate immune system and cleaves the β-(1,4) glycosidic linkages between N-acetylglucosamine (NAG) and N-acetylmuramic acid (NAM) in bacterial peptidoglycan (see Chemical Defenses). Additionally, fluids containing immunoglobulins and phagocytic cells are produced in the gingival spaces. Despite all of these chemical and mechanical activities, the mouth supports a large microbial community.

**Exercise 11.1.2**

What factors make the mouth inhospitable for certain microbes?

## Anatomy and Normal Microbiota of the GI Tract

As food leaves the oral cavity, it travels through the pharynx, or the back of the throat, and moves into the esophagus, which carries the food from the pharynx to the stomach without adding any additional digestive enzymes. The stomach produces mucus to protect its lining, as well as digestive enzymes and acid to break down food. Partially digested food then leaves the stomach through the pyloric sphincter, reaching the first part of the small intestine called the duodenum. Pancreatic juice, which includes enzymes and bicarbonate ions, is released into the small intestine to neutralize the acidic material from the stomach and to assist in digestion. Bile, produced by the liver but stored in the gallbladder, is also released into the small intestine to emulsify fats so that they can travel in the watery environment of the small intestine. Digestion continues in the small intestine, where the majority of nutrients contained in the food are absorbed. Simple columnar epithelial cells called enterocytes line the lumen surface of the small intestinal folds called villi. Each enterocyte has smaller microvilli (cytoplasmic membrane extensions) on the cellular apical surface that increase the surface area to allow more absorption of nutrients to occur (Figure 11.1.4).

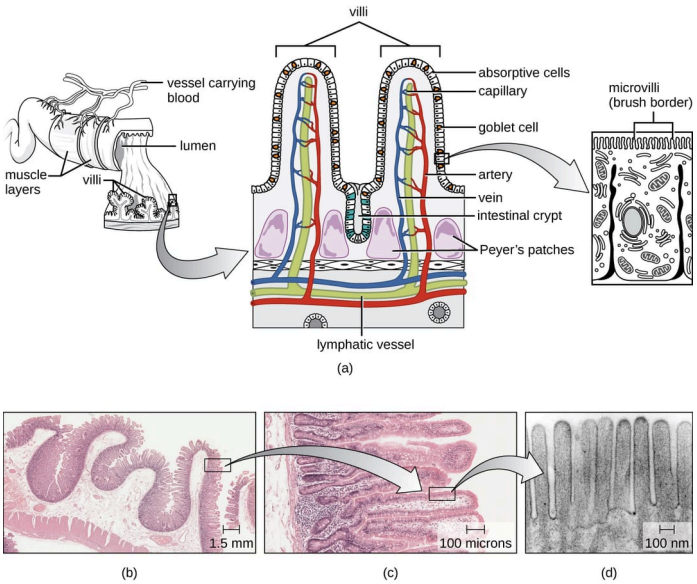



Figure 11.1.4: (a) The structure of the wall of the small intestine allows for the majority of nutrient absorption in the body. (b) Villi are folds in the surface of the small intestine. Microvilli are cytoplasmic extensions on individual cells that increase the surface area for absorption. (c) A light micrograph shows the shape of the villi. (d) An electron micrograph shows the shape of the microvilli. (credit b, c, d: Modification of micrographs provided by the Regents of University of Michigan Medical School © 2012)

Digested food leaves the small intestine and moves into the large intestine, or colon, where there is a more diverse microbiota. Near this junction, there is a small pouch in the large intestine called the cecum, which attaches to the appendix. Further digestion occurs throughout the colon and water is reabsorbed, then waste is excreted through the rectum, the last section of the colon, and out of the body through the anus (Figure 11.1.1).

The environment of most of the GI tract is harsh, which serves two purposes: digestion and immunity. The stomach is an extremely acidic environment (pH 1.5–3.5) due to the gastric juices that break down food and kill many ingested microbes; this helps prevent infection from pathogens. The environment in the small intestine is less harsh and is able to support microbial communities. Microorganisms present in the small intestine can include lactobacilli, diptherioids and the fungus *Candida*. On the other hand, the large intestine (colon) contains a diverse and abundant microbiota that is important for normal function. These microbes include *Bacteriodetes* (especially the genera *Bacteroides* and *Prevotella*) and *Firmicutes* (especially members of the genus *Clostridium*). Methanogenic archaea and some fungi are also present, among many other species of bacteria. These microbes all aid in digestion and contribute to the production of feces, the waste excreted from the digestive tract, and flatus, the gas produced from microbial fermentation of undigested food. They can also produce valuable nutrients. For example, lactic acid bacteria such as bifidobacteria can synthesize vitamins, such as vitamin B12, folate, and riboflavin, that humans cannot synthesize themselves. *E. coli* found in the intestine can also break down food and help the body produce vitamin K, which is important for blood coagulation.

The GI tract has several other methods of reducing the risk of infection by pathogens. Small aggregates of underlying lymphoid tissue in the ileum, called Peyer's patches (Figure 11.1.4), detect pathogens in the intestines via microfold (M) cells, which transfer antigens from the lumen of the intestine to the lymphocytes on Peyer's patches to induce an immune response. The Peyer's patches then secrete IgA and other pathogen-specific antibodies into the intestinal lumen to help keep intestinal microbes at safe levels. Goblet cells, which are modified simple columnar epithelial cells, also line the GI tract (Figure 11.1.5). Goblet cells secrete a gel-forming mucin, which is the major component of mucus. The production of a protective layer of mucus helps reduce the risk of pathogens reaching deeper tissues.

The constant movement of materials through the gastrointestinal tract also helps to move transient pathogens out of the body. In fact, feces are composed of approximately 25% microbes, 25% sloughed epithelial cells, 25% mucus, and 25% digested or undigested food. Finally, the normal microbiota provides an additional barrier to infection via a variety of mechanisms. For example, these organisms outcompete potential pathogens for space and nutrients within the intestine. This is known as competitive exclusion. Members of the microbiota may also secrete protein toxins known as bacteriocins that are able to bind to specific receptors on the surface of susceptible bacteria.

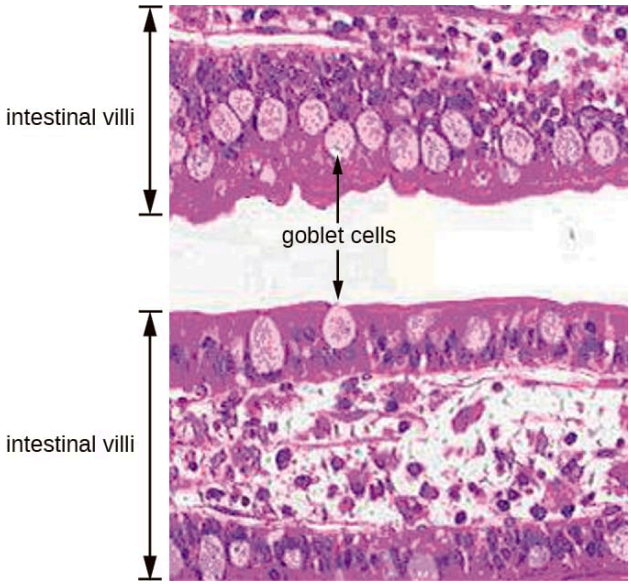



Figure 11.1.5: A magnified image of intestinal villi in the GI tract shows goblet cells. These cells are important in producing a protective layer of mucus.

**Exercise 11.1.3**

Compare and contrast the microbiota of the small and large intestines.

## General Signs and Symptoms of Oral and GI Disease

Despite numerous defense mechanisms that protect against infection, all parts of the digestive tract can become sites of infection or intoxication. The term food poisoning is sometimes used as a catch-all for GI infections and intoxications, but not all forms of GI disease originate with foodborne pathogens or toxins.

In the mouth, fermentation by anaerobic microbes produces acids that damage the teeth and gums. This can lead to tooth decay, cavities, and periodontal disease, a condition characterized by chronic inflammation and erosion of the gums. Additionally, some pathogens can cause infections of the mucosa, glands, and other structures in the mouth, resulting in inflammation, sores, cankers, and other lesions. An open sore in the mouth or GI tract is typically called an ulcer.

Infections and intoxications of the lower GI tract often produce symptoms such as nausea, vomiting, diarrhea, aches, and fever. In some cases, vomiting and diarrhea may cause severe dehydration and other complications that can become serious or fatal. Various clinical terms are used to describe gastrointestinal symptoms. For example, gastritis is an inflammation of the stomach lining that results in swelling and enteritis refers to inflammation of the intestinal mucosa. When the inflammation involves both the stomach lining and the intestinal lining, the condition is called gastroenteritis. Inflammation of the liver is called hepatitis. Inflammation of the colon, called colitis, commonly occurs in cases of food intoxication. Because an inflamed colon does not reabsorb water as effectively as it normally does, stools become watery, causing diarrhea. Damage to the epithelial cells of the colon can also cause bleeding and excess mucus to appear in watery stools, a condition called dysentery.

**Exercise 11.1.4**

List possible causes and signs and symptoms of food poisoning.

## Key Concepts and Summary

- The digestive tract, consisting of the oral cavity, pharynx, esophagus, stomach, small intestine, and large intestine, has a normal microbiota that is important for health.

- The constant movement of materials through the gastrointestinal canal, the protective layer of mucus, the normal microbiota, and the harsh chemical environment in the stomach and small intestine help to prevent colonization by pathogens.
- Infections or microbial toxins in the oral cavity can cause **tooth decay**, **periodontal disease**, and various types of **ulcers**.
- Infections and intoxications of the gastrointestinal tract can cause general symptoms such as nausea, vomiting, diarrhea, and fever. Localized inflammation of the GI tract can result in **gastritis**, **enteritis**, **gastroenteritis**, **hepatitis**, or **colitis**, and damage to epithelial cells of the colon can lead to **dysentery**.
- **Foodborne illness** refers to infections or intoxications that originate with pathogens or toxins ingested in contaminated food or water.

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# 11.2: Microbial Diseases of the Mouth and Oral Cavity

**Learning Objectives**

- Explain the role of microbial activity in diseases of the mouth and oral cavity
- Compare the major characteristics of specific oral diseases and infections

Despite the presence of saliva and the mechanical forces of chewing and eating, some microbes thrive in the mouth. These microbes can cause damage to the teeth and can cause infections that have the potential to spread beyond the mouth and sometimes throughout the body.

## Dental Caries

Cavities of the teeth, known clinically as dental caries, are microbial lesions that cause damage to the teeth. Over time, the lesion can grow through the outer enamel layer to infect the underlying dentin or even the innermost pulp. If dental caries are not treated, the infection can become an abscess that spreads to the deeper tissues of the teeth, near the roots, or to the bloodstream.

Tooth decay results from the metabolic activity of microbes that live on the teeth. A layer of proteins and carbohydrates forms when clean teeth come into contact with saliva. Microbes are attracted to this food source and form a biofilmcalled plaque. The most important cariogenic species in these biofilms is *Streptococcus mutans*. When sucrose, a disaccharide sugar from food, is broken down by bacteria in the mouth, glucose and fructose are produced. The glucose is used to make dextran, which is part of the extracellular matrix of the biofilm. Fructose is fermented, producing organic acids such as lactic acid. These acids dissolve the minerals of the tooth, including enamel, even though it is the hardest material in the body. The acids work even more quickly on exposed dentin (Figure 11.2.1). Over time, the plaque biofilm can become thick and eventually calcify. When a heavy plaque deposit becomes hardened in this way, it is called tartar or dental calculus (Figure 11.2.2). These substantial plaque biofilms can include a variety of bacterial species, including *Streptococcus* and *Actinomyces* species.

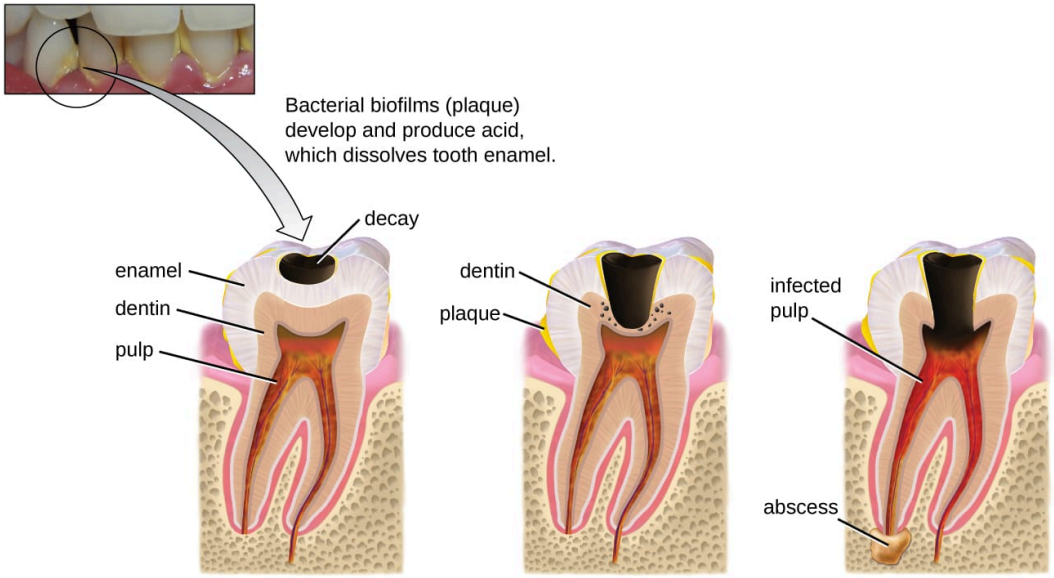



Figure 11.2.1: Tooth decay occurs in stages. When bacterial biofilms (plaque) develop on teeth, the acids produced gradually dissolve the enamel, followed by the dentin. Eventually, if left untreated, the lesion may reach the pulp and cause an abscess. (credit: modification of work by “BruceBlaus”/Wikimedia Commons)

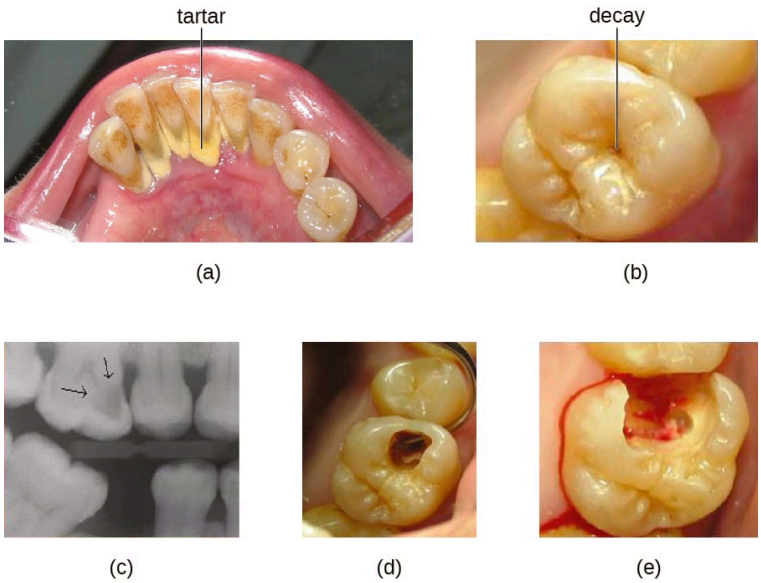



Figure 11.2.2: (a) Tartar (dental calculus) is visible at the bases of these teeth. The darker deposits higher on the crowns are staining. (b) This tooth shows only a small amount of visible decay. (c) An X-ray of the same tooth shows that there is a dark area representing more decay inside the tooth. (d) Removal of a portion of the crown reveals the area of damage. (e) All of the cavity must be removed before filling. (credit: modification of work by "DRosenbach"/Wikimedia Commons)

Some tooth decay is visible from the outside, but it is not always possible to see all decay or the extent of the decay. X-ray imaging is used to produce radiographs that can be studied to look for deeper decay and damage to the root or bone (Figure 11.2.2). If not detected, the decay can reach the pulp or even spread to the bloodstream. Painful abscesses can develop.

To prevent tooth decay, prophylactic treatment and good hygiene are important. Regular tooth brushing and flossing physically removes microbes and combats microbial growth and biofilm formation. Toothpaste contains fluoride, which becomes incorporated into the hydroxyapatite of tooth enamel, protecting it against acidity caused by fermentation of mouth microbiota. Fluoride is also bacteriostatic, thus slowing enamel degradation. Antiseptic mouthwashes commonly contain plant-derived phenolics like thymol and eucalyptol and/or heavy metals like zinc chloride (see Using Chemicals to Control Microorganisms). Phenolics tend to be stable and persistent on surfaces, and they act through denaturing proteins and disrupting membranes.

Regular dental cleanings allow for the detection of decay at early stages and the removal of tartar. They may also help to draw attention to other concerns, such as damage to the enamel from acidic drinks. Reducing sugar consumption may help prevent damage that results from the microbial fermentation of sugars. Additionally, sugarless candies or gum with sugar alcohols (such as xylitol) can reduce the production of acids because these are fermented to nonacidic compounds (although excess consumption may lead to gastrointestinal distress). Fluoride treatment or ingesting fluoridated water strengthens the minerals in teeth and reduces the incidence of dental caries.

If caries develop, prompt treatment prevents worsening. Smaller areas of decay can be drilled to remove affected tissue and then filled. If the pulp is affected, then a root canal may be needed to completely remove the infected tissues to avoid continued spread of the infection, which could lead to painful abscesses.

### Exercise 11.2.1

1. Name some ways that microbes contribute to tooth decay.
2. What is the most important cariogenic species of bacteria?

*Answer available at the end of this section.*

## Periodontal Disease

In addition to damage to the teeth themselves, the surrounding structures can be affected by microbes. Periodontal disease is the result of infections that lead to inflammation and tissue damage in the structures surrounding the teeth. The progression

from mild to severe periodontal disease is generally reversible and preventable with good oral hygiene.

Inflammation of the gums that can lead to irritation and bleeding is called gingivitis. When plaque accumulates on the teeth, bacteria colonize the gingival space. As this space becomes increasingly blocked, the environment becomes anaerobic. This allows a wide variety of microbes to colonize, including *Porphyromonas*, *Streptococcus*, and *Actinomyces*. The bacterial products, which include lipopolysaccharide (LPS), proteases, lipoteichoic acids, and others, cause inflammation and gum damage (Figure 11.2.3). It is possible that methanogenic archaeans (including *Methanobrevibacter oralis* and other *Methanobrevibacter* species) also contribute to disease progression as some species have been identified in patients with periodontal disease, but this has proven difficult to study.[123] Gingivitis is diagnosed by visual inspection, including measuring pockets in the gums, and X-rays, and is usually treated using good dental hygiene and professional dental cleaning, with antibiotics reserved for severe cases.



Figure 11.2.3: Redness and irritation of the gums are evidence of gingivitis.

Over time, chronic gingivitis can develop into the more serious condition of periodontitis (Figure 11.2.4). When this happens, the gums recede and expose parts of the tooth below the crown. This newly exposed area is relatively unprotected, so bacteria can grow on it and spread underneath the enamel of the crown and cause cavities. Bacteria in the gingival space can also erode the cementum, which helps to hold the teeth in place. If not treated, erosion of cementum can lead to the movement or loss of teeth. The bones of the jaw can even erode if the infection spreads. This condition can be associated with bleeding and halitosis (bad breath). Cleaning and appropriate dental hygiene may be sufficient to treat periodontitis. However, in cases of severe periodontitis, an antibiotic may be given. Antibiotics may be given in pill form or applied directly to the gum (local treatment). Antibiotics given can include tetracycline, doxycycline, macrolides or β-lactams. Because periodontitis can be caused by a mix of microbes, a combination of antibiotics may be given.

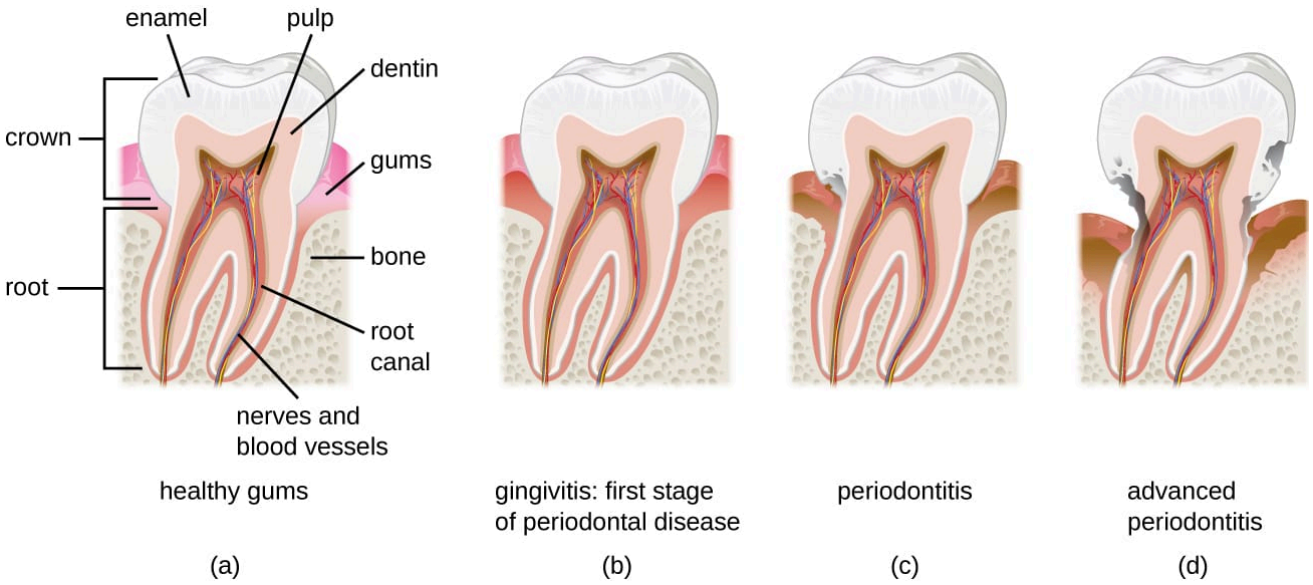



Figure 11.2.4: (a) Healthy gums hold the teeth firmly and do not bleed. (b) Gingivitis is the first stage of periodontal disease. Microbial infection causes gums to become inflamed and irritated, with occasional bleeding. (c) In periodontitis, gums recede and expose parts of the tooth normally covered. (d) In advanced periodontitis, the infection spreads to ligaments and bone tissue supporting the teeth. Tooth loss may occur, or teeth may need to be surgically removed. (credit: modification of work by "BruceBlaus"/Wikimedia Commons)

## Trench Mouth

When certain bacteria, such as *Prevotella intermedia*, *Fusobacterium* species, and *Treponema vicentii*, are involved and periodontal disease progresses, acute necrotizing ulcerative gingivitis or trench mouth, also called Vincent's disease, can develop. This is severe periodontitis characterized by erosion of the gums, ulcers, substantial pain with chewing, and halitosis (Figure 11.2.5 ) that can be diagnosed by visual examination and X-rays. In countries with good medical and dental care, it is most common in individuals with weakened immune systems, such as patients with AIDS. In addition to cleaning and pain medication, patients may be prescribed antibiotics such as amoxicillin, amoxicillin clavulanate, clindamycin, or doxycycline.



Figure 11.2.5: These inflamed, eroded gums are an example of a mild case of acute necrotizing ulcerative gingivitis, also known as trench mouth. (credit: modification of work by Centers for Disease Control and Prevention)

**Exercise 11.2.2**

How does gingivitis progress to periodontitis?

**Healthy Mouth, Healthy Body**

Good oral health promotes good overall health, and the reverse is also true. Poor oral health can lead to difficulty eating, which can cause malnutrition. Painful or loose teeth can also cause a person to avoid certain foods or eat less. Malnutrition due to dental problems is of greatest concern for the elderly, for whom it can worsen other health conditions and contribute to mortality. Individuals who have serious illnesses, especially AIDS, are also at increased risk of malnutrition from dental problems.

Additionally, poor oral health can contribute to the development of disease. Increased bacterial growth in the mouth can cause inflammation and infection in other parts of the body. For example, *Streptococcus* in the mouth, the main contributor to biofilms on teeth, tartar, and dental caries, can spread throughout the body when there is damage to the tissues inside the mouth, as can happen during dental work. *S. mutans* produces a surface adhesin known as P1, which binds to salivary agglutinin on the surface of the tooth. P1 can also bind to extracellular matrix proteins including fibronectin and collagen. When *Streptococcus* enters the bloodstream as a result of tooth brushing or dental cleaning, it causes inflammation that can lead to the accumulation of plaque in the arteries and contribute to the development of atherosclerosis, a condition associated with cardiovascular disease, heart attack, and stroke. In some cases, bacteria that spread through the blood vessels can lodge in the heart and cause endocarditis (an example of a focal infection).

## Oral Infections

As noted earlier, normal oral microbiota can cause dental and periodontal infections. However, there are number of other infections that can manifest in the oral cavity when other microbes are present.

## Herpetic Gingivostomatitis

As described in Viral Infections of the Skin and Eyes, infections by herpes simplex virus type 1 (HSV-1) frequently manifest as oral herpes, also called acute herpes labialis and characterized by cold sores on the lips, mouth, or gums. HSV-1 can also cause acute herpetic gingivostomatitis, a condition that results in ulcers of the mucous membranes inside the mouth (Figure 11.2.6 ). Herpetic gingivostomatitis is normally self-limiting except in immunocompromised patients. Like oral herpes, the infection is generally diagnosed through clinical examination, but cultures or biopsies may be obtained if other signs or symptoms suggest the possibility of a different causative agent. If treatment is needed, mouthwashes or antiviral medications such as acyclovir, famciclovir, or valacyclovir may be used.

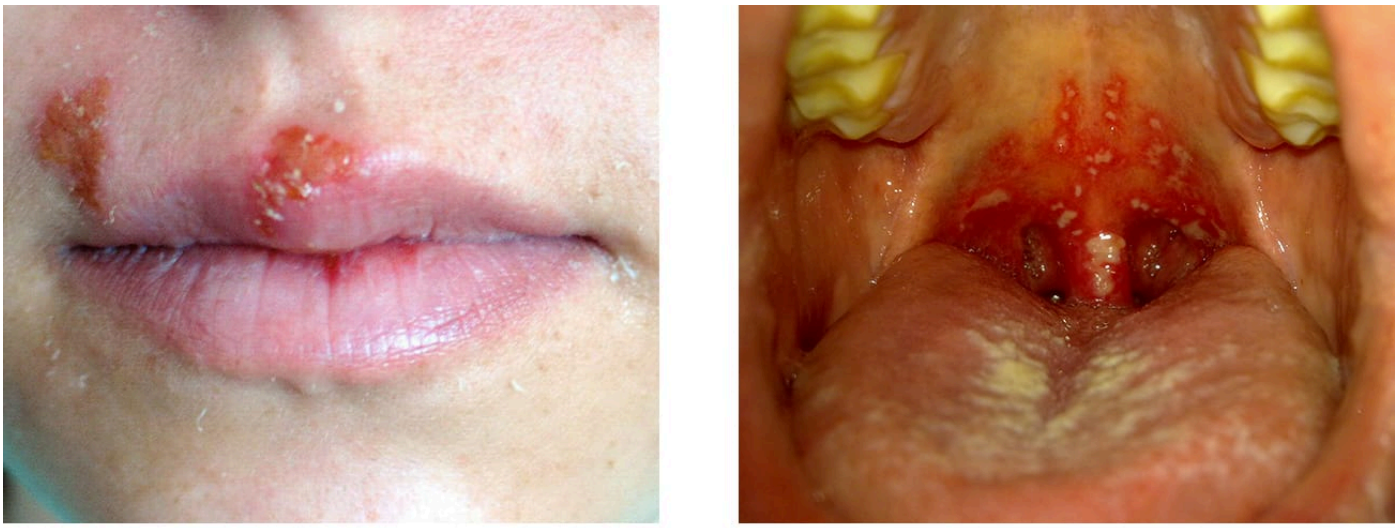



Figure 11.2.6: (a) This cold sore is caused by infection with herpes simplex virus type 1 (HSV-1). (b) HSV-1 can also cause acute herpetic gingivostomatitis. (credit b: modification of work by Klaus D. Peter)

## Oral Thrush

The yeast *Candida* is part of the normal human microbiota, but overgrowths, especially of *Candida albicans*, can lead to infections in several parts of the body. When *Candida* infection develops in the oral cavity, it is called oral thrush. Oral thrush is most common in infants because they do not yet have well developed immune systems and have not acquired the robust normal microbiota that keeps *Candida* in check in adults. Oral thrush is also common in immunodeficient patients and is a common infection in patients with AIDS.

Oral thrush is characterized by the appearance of white patches and pseudomembranes in the mouth (Figure 11.2.7) and can be associated with bleeding. The infection may be treated topically with nystatin or clotrimazole oral suspensions, although systemic treatment is sometimes needed. In serious cases, systemic azoles such as fluconazole or itraconazole (for strains resistant to fluconazole), may be used. Amphotericin B can also be used if the infection is severe or if the *Candida* species is azole-resistant.

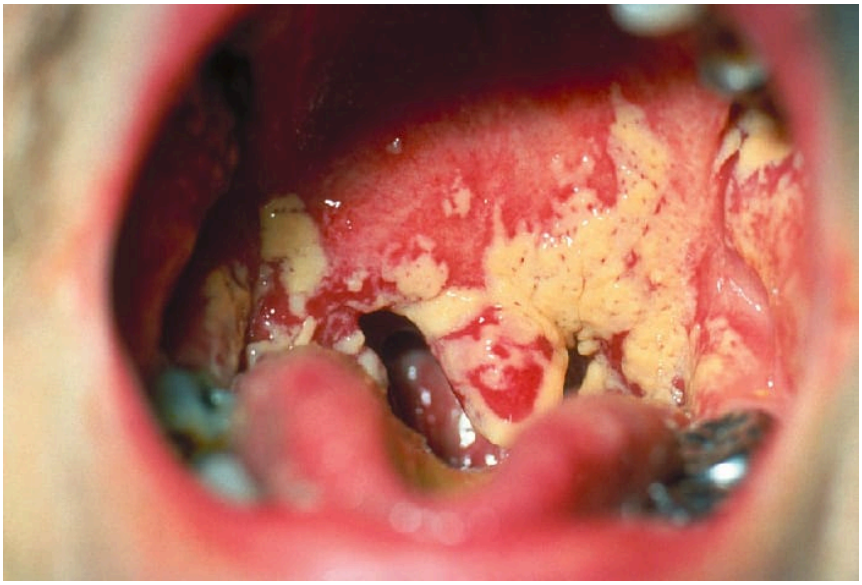


Figure 11.2.7: Overgrowth of *Candida* in the mouth is called thrush. It often appears as white patches. (credit: modification of work by Centers for Disease Control and Prevention)

## Mumps

The viral disease mumps is an infection of the parotid glands, the largest of the three pairs of salivary glands (Figure 24.1.2). The causative agent is mumps virus (MuV), a paramyxovirus with an envelope that has hemagglutinin and neuraminidase spikes. A fusion protein located on the surface of the envelope helps to fuse the viral envelope to the host cell plasma membrane.

Mumps virus is transmitted through respiratory droplets or through contact with contaminated saliva, making it quite contagious so that it can lead easily to epidemics. It causes fever, muscle pain, headache, pain with chewing, loss of appetite, fatigue, and weakness. There is swelling of the salivary glands and associated pain (Figure 11.2.8). The virus can enter the bloodstream (viremia), allowing it to spread to the organs and the central nervous system. The infection ranges from subclinical cases to cases with serious complications, such as encephalitis, meningitis, and deafness. Inflammation of the pancreas, testes, ovaries, and breasts may also occur and cause permanent damage to those organs; despite these complications, a mumps infection rarely cause sterility.

Mumps can be recognized based on clinical signs and symptoms, and a diagnosis can be confirmed with laboratory testing. The virus can be identified using culture or molecular techniques such as RT-PCR. Serologic tests are also available, especially enzyme immunoassays that detect antibodies. There is no specific treatment for mumps, so supportive therapies are used. The most effective way to avoid infection is through vaccination. Although mumps used to be a common childhood disease, it is now rare in the United States due to vaccination with the measles, mumps, and rubella (MMR) vaccine.

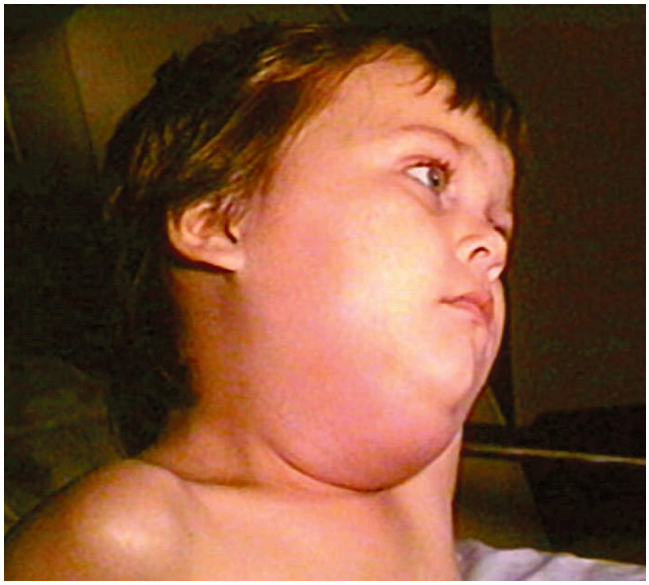


Figure 11.2.8: This child shows the characteristic parotid swelling associated with mumps. (credit: modification of work by Centers for Disease Control and Prevention)

### Exercise 11.2.3

Compare and contrast the signs and symptoms of herpetic gingivostomatitis, oral thrush, and mumps.

### Oral Infections

Infections of the mouth and oral cavity can be caused by a variety of pathogens, including bacteria, viruses, and fungi. Many of these infections only affect the mouth, but some can spread and become systemic infections. Figure 11.2.9 summarizes the main characteristics of common oral infections.

| Oral Infections | | | | | |
|---|---|---|---|---|---|
| Disease | Pathogen | Signs and Symptoms | Transmission | Diagnostic Tests | Antimicrobial Drugs |
| Dental caries | *Streptococcus mutans* | Discoloration, softening, cavities in teeth | Non-transmissible; caused by bacteria of the normal oral microbiota | Visual examinations, X-rays | Oral antiseptics (e.g., Listerine) |
| Gingivitis and periodontitis | *Porphyromonas*, *Streptococcus*, *Actinomyces* | Inflammation and erosion of gums, bleeding, halitosis; erosion of cementum, leading to tooth loss in advanced infections | Non-transmissible; caused by bacteria of the normal oral microbiota | Visual examination, X-rays, measuring pockets in gums | Tetracycline, doxycycline, macrolides or beta-lactams. Mixture of antibiotics may be given. |
| Herpetic gingivostomatitis | Herpes simplex virus type 1 (HSV-1) | Lesions in mucous membranes of mouth | Contact with saliva or lesions of an infected person | Culture or biopsy | Acyclovir, famcyclovir, valacyclovir |
| Mumps | Mumps virus (a paramyxovirus) | Swelling of parotid glands, fever, headache, muscle pain, weakness, fatigue, loss of appetite, pain while chewing; in serious cases, encephalitis, meningitis, and inflammation of testes, ovaries, and breasts | Contact with saliva or respiratory droplets of an infected person | Virus culture or serologic tests for antibodies, enzyme immunoassay, RT-PCR | None for treatment; MMR vaccine for prevention |
| Oral thrush | *Candida albicans*, other *Candida* spp. | White patches and pseudomembranes in mouth, may cause bleeding | Non-transmissible; caused by overgrowth of *Candida* spp. in the normal oral microbiota; primarily affects infants and the immuno-compromised | Microscopic analysis of oral samples | Clotrimazole, nystatin, fluconazole, or itraconazole; amphotericin B in severe cases |
| Trench mouth (acute necrotizing ulcerative gingivitis) | *Prevotella intermedia* *Fusobacterium* species, *Treponema vincentii*, others | Erosion of gums, ulcers, substantial pain with chewing, halitosis | Non-transmissible; caused by members of the normal oral microbiota | Visual examinations, X-rays | Amoxicillin, amoxicillin clavulanate, clindamycin, or doxycycline |

Figure 11.2.9: Oral infections.

## Key Concepts and Summary

- **Dental caries**, **tartar**, and **gingivitis** are caused by overgrowth of oral bacteria, usually *Streptococcus* and *Actinomyces* species, as a result of insufficient dental hygiene.
- Gingivitis can worsen, allowing *Porphyromonas*, *Streptococcus*, and *Actinomyces* species to spread and cause **periodontitis**. When *Prevotella intermedia*, *Fusobacterium* species, and *Treponema vicentii* are involved, it can lead to **acute necrotizing ulcerative gingivitis**.
- The herpes simplex virus type 1 can cause lesions of the mouth and throat called **herpetic gingivostomatitis.**
- Other infections of the mouth include **oral thrush**, a fungal infection caused by overgrowth of *Candida* yeast, and **mumps**, a viral infection of the salivary glands caused by the mumps virus, a paramyxovirus.

## Footnotes

1. 1 Hans-Peter Horz and Georg Conrads. “Methanogenic *Archaea* and Oral Infections—Ways to Unravel the Black Box.” *Journal of Oral Microbiology* 3(2011). doi: 10.3402/jom.v3i0.5940.
2. 2 Hiroshi Maeda, Kimito Hirai, Junji Mineshiba, Tadashi Yamamoto, Susumu Kokeguchi, and Shogo Takashiba. “Medical Microbiological Approach to Archaea in Oral Infectious Diseases.” *Japanese Dental Science Review* 49: 2, p. 72–78.
3. 3 Paul W. Lepp, Mary M. Brinig, Cleber C. Ouverney, Katherine Palm, Gary C. Armitage, and David A. Relman. “Methanogenic *Archaea* and Human Periodontal Disease.” *Proceedings of the National Academy of Sciences of the United States of America* 101 (2003): 16, pp. 6176–6181. doi: 10.1073/pnas.0308766101.

## Answers

**Exercise** 11.2.1

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# 11.3: Bacterial Infections of the Gastrointestinal Tract

**Learning Objectives**

- Identify the most common bacteria that can cause infections of the GI tract
- Compare the major characteristics of specific bacterial diseases affecting the GI tract

A wide range of gastrointestinal diseases are caused by bacterial contamination of food. Recall that foodborne diseasecan arise from either infection or intoxication. In both cases, bacterial toxins are typically responsible for producing disease signs and symptoms. The distinction lies in where the toxins are produced. In an infection, the microbial agent is ingested, colonizes the gut, and then produces toxins that damage host cells. In an intoxication, bacteria produce toxins in the food before it is ingested. In either case, the toxins cause damage to the cells lining the gastrointestinal tract, typically the colon. This leads to the common signs and symptoms of diarrhea or watery stool and abdominal cramps, or the more severe dysentery. Symptoms of foodborne diseases also often include nausea and vomiting, which are mechanisms the body uses to expel the toxic materials.

Most bacterial gastrointestinal illness is short-lived and self-limiting; however, loss of fluids due to severe diarrheal illness can lead to dehydration that can, in some cases, be fatal without proper treatment. Oral rehydration therapy with electrolyte solutions is an essential aspect of treatment for most patients with GI disease, especially in children and infants.

## Staphylococcal Food Poisoning

Staphylococcal food poisoning is one form of food intoxication. When *Staphylococcus aureus* grows in food, it may produce enterotoxins that, when ingested, can cause symptoms such as nausea, diarrhea, cramping, and vomiting within one to six hours. In some severe cases, it may cause headache, dehydration, and changes in blood pressure and heart rate. Signs and symptoms resolve within 24 to 48 hours. *S. aureus* is often associated with a variety of raw or undercooked and cooked foods including meat (e.g., canned meat, ham, and sausages) and dairy products (e.g., cheeses, milk, and butter). It is also commonly found on hands and can be transmitted to prepared foods through poor hygiene, including poor handwashing and the use of contaminated food preparation surfaces, such as cutting boards. The greatest risk is for food left at a temperature below 60 °C (140 °F), which allows the bacteria to grow. Cooked foods should generally be reheated to at least 60 °C (140 °F) for safety and most raw meats should be cooked to even higher internal temperatures (Figure 11.3.1).

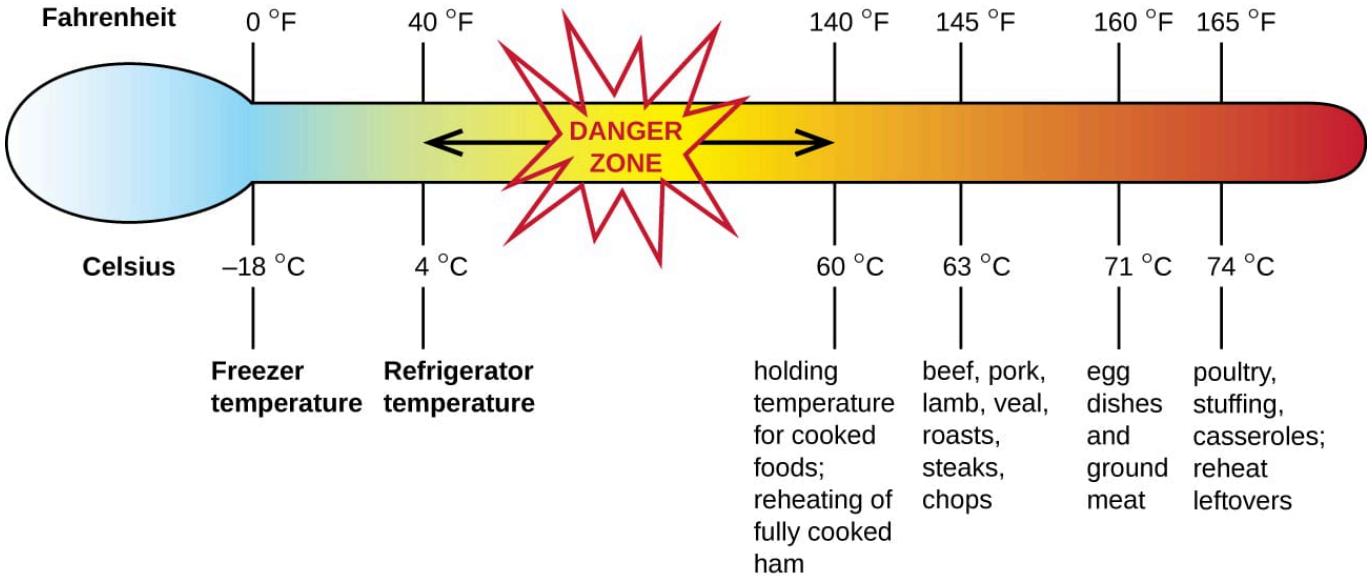



Figure 11.3.1: This figure indicates safe internal temperatures associated with the refrigeration, cooking, and reheating of different foods. Temperatures above refrigeration and below the minimum cooking temperature may allow for microbial growth, increasing the likelihood of foodborne disease. (credit: modification of work by USDA)

There are at least 21 *Staphylococcal* enterotoxins and *Staphylococcal* enterotoxin-like toxins that can cause food intoxication. The enterotoxins are proteins that are resistant to low pH, allowing them to pass through the stomach. They are heat stable and are not destroyed by boiling at 100 °C. Even though the bacterium itself may be killed, the enterotoxins alone can cause vomiting and diarrhea, although the mechanisms are not fully understood. At least some of the symptoms may be caused by the enterotoxin functioning as a superantigen and provoking a strong immune response by activating T cell proliferation.

The rapid onset of signs and symptoms helps to diagnose this foodborne illness. Because the bacterium does not need to be present for the toxin to cause symptoms, diagnosis is confirmed by identifying the toxin in a food sample or in biological specimens (feces or vomitus) from the patient. Serological techniques, including ELISA, can also be used to identify the toxin in food samples.

The condition generally resolves relatively quickly, within 24 hours, without treatment. In some cases, supportive treatment in a hospital may be needed.

**Exercise 11.3.1**

How can S. *aureus* cause food intoxication?

## Shigellosis (Bacillary Dysentery)

When gastrointestinal illness is associated with the rod-shaped, gram-negative bacterium *Shigella*, it is called bacillary dysentery, or shigellosis. Infections can be caused by *S. dysenteriae*, *S. flexneri*, *S. boydii*, and/or *S. sonnei* that colonize the GI tract. Shigellosis can be spread from hand to mouth or through contaminated food and water. Most commonly, it is transmitted through the fecal-oral route.

*Shigella* bacteria invade intestinal epithelial cells. When taken into a phagosome, they can escape and then live within the cytoplasm of the cell or move to adjacent cells. As the organisms multiply, the epithelium and structures with M cells of the Peyer's patches in the intestine may become ulcerated and cause loss of fluid. Stomach cramps, fever, and watery diarrhea that may also contain pus, mucus, and/or blood often develop. More severe cases may result in ulceration of the mucosa, dehydration, and rectal bleeding. Additionally, patients may later develop hemolytic uremic syndrome (HUS), a serious condition in which damaged blood cells build up in the kidneys and may cause kidney failure, or reactive arthritis, a condition in which arthritis develops in multiple joints following infection. Patients may also develop chronic post-infection irritable bowel syndrome (IBS).

*S. dysenteriae* type 1 is able to produce Shiga toxin, which targets the endothelial cells of small blood vessels in the small and large intestine by binding to a glycosphingolipid. Once inside the endothelial cells, the toxin targets the large ribosomal subunit, thus affecting protein synthesis of these cells. Hemorrhaging and lesions in the colon can result. The toxin can target the kidney's glomerulus, the blood vessels where filtration of blood in the kidney begins, thus resulting in HUS.

Stool samples, which should be processed promptly, are analyzed using serological or molecular techniques. One common method is to perform immunoassays for *S. dysenteriae*. (Other methods that can be used to identify *Shigella* include API test strips, Enterotube systems, or PCR testing. The presence of white blood cells and blood in fecal samples occurs in about 70% of patients[1] (Figure 11.3.2). Severe cases may require antibiotics such as ciprofloxacin and azithromycin, but these must be carefully prescribed because resistance is increasingly common.

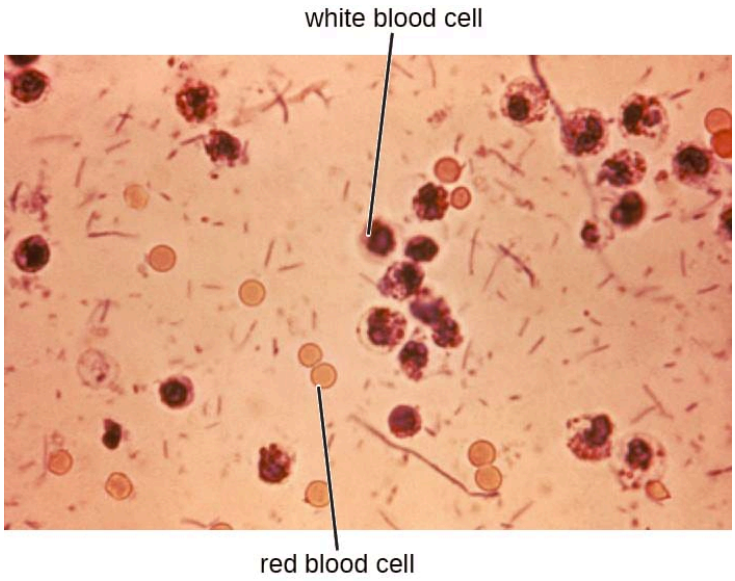



Figure 11.3.2: Red and white blood cells can be seen in this micrograph of a stool sample from a patient with shigellosis.

**Exercise 11.3.2**

Compare and contrast *Shigella* infections and intoxications.

## Salmonellosis

*Salmonella* gastroenteritis, also called salmonellosis, is caused by the rod-shaped, gram-negative bacterium *Salmonella*. Two species, *S. enterica* and *S. bongori*, cause disease in humans, but *S. enterica* is the most common. The most common serotypes of *S. enterica* are Enteritidis and Typhi. We will discuss typhoid fever caused by serotypes Typhi and Paratyphi A separately. Here, we will focus on salmonellosis caused by other serotypes.

*Salmonella* is a part of the normal intestinal microbiota of many individuals. However, salmonellosis is caused by exogenous agents, and infection can occur depending on the serotype, size of the inoculum, and overall health of the host. Infection is caused by ingestion of contaminated food, handling of eggshells, or exposure to certain animals. *Salmonella* is part of poultry's microbiota, so exposure to raw eggs and raw poultry can increase the risk of infection. Handwashing and cooking foods thoroughly greatly reduce the risk of transmission. *Salmonella* bacteria can survive freezing for extended periods but cannot survive high temperatures.

Once the bacteria are ingested, they multiply within the intestines and penetrate the epithelial mucosal cells via M cells where they continue to grow (Figure 11.3.3). They trigger inflammatory processes and the hypersecretion of fluids. Once inside the body, they can persist inside the phagosomes of macrophages. *Salmonella* can cross the epithelial cell membrane and enter the bloodstream and lymphatic system. Some strains of *Salmonella* also produce an enterotoxin that can cause an intoxication.

Infected individuals develop fever, nausea, abdominal cramps, vomiting, headache, and diarrhea. These signs and symptoms generally last a few days to a week. According to the Centers for Disease Control and Prevention (CDC), there are 1,000,000 cases annually, with 380 deaths each year.[2] However, because the disease is usually self-limiting, many cases are not reported to doctors and the overall incidence may be underreported. Diagnosis involves culture followed by serotyping and DNA fingerprinting if needed. Positive results are reported to the CDC. When an unusual serotype is detected, samples are sent to the CDC for further analysis. Serotyping is important for determining treatment. Oral rehydration therapy is commonly used. Antibiotics are only recommended for serious cases. When antibiotics are needed, as in immunocompromised patients, fluoroquinolones, third-generation cephalosporins, and ampicillin are recommended. Antibiotic resistance is a serious concern.



Figure 11.3.3: Salmonella entering an intestinal epithelial cell by reorganizing the host cell's cytoskeleton via the trigger mechanism. (credit: modification of work by National Institutes for Health)

## Typhoid Fever

Certain serotypes of *S. enterica*, primarily serotype Typhi (*S. typhi*) but also Paratyphi, cause a more severe type of salmonellosis called typhoid fever. This serious illness, which has an untreated mortality rate of 10%, causes high fever, body aches, headache, nausea, lethargy, and a possible rash.

Some individuals carry *S. typhi* without presenting signs or symptoms (known as asymptomatic carriers) and continually shed them through their feces. These carriers often have the bacteria in the gallbladder or intestinal epithelium. Individuals consuming food or water contaminated with these feces can become infected.

*S. typhi* penetrate the intestinal mucosa, grow within the macrophages, and are transported through the body, most notably to the liver and gallbladder. Eventually, the macrophages lyse, releasing *S. typhi* into the bloodstream and lymphatic system. Mortality can result from ulceration and perforation of the intestine. A wide range of complications, such as pneumonia and jaundice, can occur with disseminated disease.

*S. typhi* have *Salmonella* pathogenicity islands (SPIs) that contain the genes for many of their virulence factors. Two examples of important typhoid toxins are the Vi antigen, which encodes for capsule production, and chimeric A2B5 toxin, which causes many of the signs and symptoms of the acute phase of typhoid fever.

Clinical examination and culture are used to make the diagnosis. The bacteria can be cultured from feces, urine, blood, or bone marrow. Serology, including ELISA, is used to identify the most pathogenic strains, but confirmation with DNA testing or culture is needed. A PCR test can also be used, but is not widely available.

The recommended antibiotic treatment involves fluoroquinolones, ceftriaxone, and azithromycin. Individuals must be extremely careful to avoid infecting others during treatment. Typhoid fever can be prevented through vaccination for individuals traveling to parts of the world where it is common.

### Exercise 11.3.3

Why is serotyping particularly important in *Salmonella* infections and typhoid fever?

### Typhoid Mary

Mary Mallon was an Irish immigrant who worked as a cook in New York in the early 20th century. Over seven years, from 1900 to 1907, Mallon worked for a number of different households, unknowingly spreading illness to the people who lived in each one. In 1906, one family hired George Soper, an expert in typhoid fever epidemics, to determine the cause of the illnesses in their household. Eventually, Soper tracked Mallon down and directly linked 22 cases of typhoid fever to her. He discovered that Mallon was a carrier for typhoid but was immune to it herself. Although active carriers had been recognized before, this was the first time that an asymptomatic carrier of infection had been identified.

Because she herself had never been ill, Mallon found it difficult to believe she could be the source of the illness. She fled from Soper and the authorities because she did not want to be quarantined or forced to give up her profession, which was relatively well paid for someone with her background. However, Mallon was eventually caught and kept in an isolation facility in the Bronx, where she remained until 1910, when the New York health department released her under the condition that she never again work with food. Unfortunately, Mallon did not comply, and she soon began working as a cook again. After new cases began to appear that resulted in the death of two individuals, the authorities tracked her down again and returned her to isolation, where she remained for 23 more years until her death in 1938. Epidemiologists were able to trace 51 cases of typhoid fever and three deaths directly to Mallon, who is unflatteringly remembered as "Typhoid Mary."

The Typhoid Mary case has direct correlations in the health-care industry. Consider Kaci Hickox, an American nurse who treated Ebola patients in West Africa during the 2014 epidemic. After returning to the United States, Hickox was quarantined against her will for three days and later found not to have Ebola. Hickox vehemently opposed the quarantine. In an editorial published in the British newspaper *The Guardian*,[3] Hickox argued that quarantining asymptomatic health-care workers who had not tested positive for a disease would not only prevent such individuals from practicing their profession, but discourage others from volunteering to work in disease-ridden areas where health-care workers are desperately needed.

What is the responsibility of an individual like Mary Mallon to change her behavior to protect others? What happens when an individual believes that she is not a risk, but others believe that she is? How would you react if you were in Mallon's shoes and were placed in a quarantine you did not believe was necessary, at the expense of your own freedom and possibly your career? Would it matter if you were definitely infected or not?

## E. coli Infections

The gram-negative rod *Escherichia coli* is a common member of the normal microbiota of the colon. Although the vast majority of *E. coli* strains are helpful commensal bacteria, some can be pathogenic and may cause dangerous diarrheal disease. The pathogenic strains have additional virulence factors such as type 1 fimbriae that promote colonization of the colon or may produce toxins (see Virulence Factors of Bacterial and Viral Pathogens). These virulence factors are acquired through horizontal gene transfer.

Extraintestinal disease can result if the bacteria spread from the gastrointestinal tract. Although these bacteria can be spread from person to person, they are often acquired through contaminated food or water. There are six recognized pathogenic groups of *E. coli*, but we will focus here on the four that are most commonly transmitted through food and water.

Enterotoxigenic *E. coli* (ETEC), also known as traveler's diarrhea, causes diarrheal illness and is common in less developed countries. In Mexico, ETEC infection is called Montezuma's Revenge. Following ingestion of contaminated food or water, infected individuals develop a watery diarrhea, abdominal cramps, malaise (a feeling of being unwell), and a low fever. ETEC produces a heat-stable enterotoxin similar to cholera toxin, and adhesins called colonization factors that help the bacteria to attach to the intestinal wall. Some strains of ETEC also produce heat-labile toxins. The disease is usually relatively mild and self-limiting. Diagnosis involves culturing and PCR. If needed, antibiotic treatment with fluoroquinolones, doxycycline, rifaximin, and trimethoprim-sulfamethoxazole (TMP/SMZ) may shorten infection duration. However, antibiotic resistance is a problem.

Enteroinvasive *E. coli* (EIEC) is very similar to shigellosis, including its pathogenesis of intracellular invasion into intestinal epithelial tissue. This bacterium carries a large plasmid that is involved in epithelial cell penetration. The illness is usually self-limiting, with symptoms including watery diarrhea, chills, cramps, malaise, fever, and dysentery. Culturing and PCR testing can be used for diagnosis. Antibiotic treatment is not recommended, so supportive therapy is used if needed.

Enteropathogenic *E. coli* (EPEC) can cause a potentially fatal diarrhea, especially in infants and those in less developed countries.

Fever, vomiting, and diarrhea can lead to severe dehydration. These *E. coli* inject a protein (Tir) that attaches to the surface of the intestinal epithelial cells and triggers rearrangement of host cell actin from microvilli to pedestals. Tir also happens to be the receptor for Intimin, a surface protein produced by EPEC, thereby allowing *E. coli* to "sit" on the pedestal. The genes necessary for this pedestal formation are encoded on the locus for enterocyte effacement (LEE) pathogenicity island. As with ETEC, diagnosis involves culturing and PCR. Treatment is similar to that for ETEC.

The most dangerous strains are enterohemorrhagic *E. coli* (EHEC), which are the strains capable of causing epidemics. In particular, the strain O157:H7 has been responsible for several recent outbreaks. Recall that the O and H refer to surface antigens that contribute to pathogenicity and trigger a host immune response ("O" refers to the O-side chain of the lipopolysaccharide and the "H" refers to the flagella). Similar to EPEC, EHEC also forms pedestals. EHEC also produces a Shiga-like toxin. Because the genome of this bacterium has been sequenced, it is known that the Shiga toxin genes were most likely acquired through transduction (horizontal gene transfer). The Shiga toxin genes originated from *Shigella dysenteriae*. Prophage from a bacteriophage that previously infected *Shigella* integrated into the chromosome of *E. coli*. The Shiga-like toxin is often called verotoxin.

EHEC can cause disease ranging from relatively mild to life-threatening. Symptoms include bloody diarrhea with severe cramping, but no fever. Although it is often self-limiting, it can lead to hemorrhagic colitis and profuse bleeding. One possible complication is HUS. Diagnosis involves culture, often using MacConkey with sorbitol agar to differentiate between *E. coli* O157:H7, which does not ferment sorbitol, and other less virulent strains of *E. coli* that can ferment sorbitol.

Serological typing or PCR testing also can be used, as well as genetic testing for Shiga toxin. To distinguish EPEC from EHEC, because they both form pedestals on intestinal epithelial cells, it is necessary to test for genes encoding for both the Shiga-like toxin and for the LEE. Both EPEC and EHEC have LEE, but EPEC lacks the gene for Shiga toxin. Antibiotic therapy is not recommended and may worsen HUS because of the toxins released when the bacteria are killed, so supportive therapies must be used. Table 11.3.1 summarizes the characteristics of the four most common pathogenic groups.

*Table 11.3.1: Some Pathogenic Groups of E. coli*

| Group | Virulence Factors and Genes | Signs and Symptoms | Diagnostic Tests | Treatment |
|---|---|---|---|---|
| Enterotoxigenic *E. coli* (ETEC) | Heat stable enterotoxin similar to cholera toxin | Relatively mild, watery diarrhea | Culturing, PCR | Self-limiting; if needed, fluoroquinolones, doxycycline, rifaximin, TMP/SMZ; antibiotic resistance is a problem |
| Enteroinvasive *E. coli* (EIEC) | *Inv* (invasive plasmid) genes | Relatively mild, watery diarrhea; dysentery or inflammatory colitis may occur | Culturing, PCR; testing for *inv* gene; additional assays to distinguish from *Shigella* | Supportive therapy only; antibiotics not recommended |
| Enteropathogenic *E. coli* (EPEC) | Locus of enterocyte effacement (LEE) pathogenicity island | Severe fever, vomiting, nonbloody diarrhea, dehydration; potentially fatal | Culturing, PCR; detection of LEE lacking Shiga-like toxin genes | Self-limiting; if needed, fluoroquinolones, doxycycline, rifaximin (TMP/SMZ); antibiotic resistance is a problem |
| Enterohemorrhagic *E. coli* (EHEC) | Verotoxin | May be mild or very severe; bloody diarrhea; may result in HUS | Culturing; plate on MacConkey agar with sorbitol agar as it does not ferment sorbitol; PCR detection of LEE containing Shiga-like toxin genes | Antibiotics are not recommended due to the risk of HUS |

## Exercise 11.3.4

Compare and contrast the virulence factors and signs and symptoms of infections with the four main *E. coli* groups.

## Cholera and Other Vibrios

The gastrointestinal disease cholera is a serious infection often associated with poor sanitation, especially following natural disasters, because it is spread through contaminated water and food that has not been heated to temperatures high enough to kill the bacteria. It is caused by *Vibrio cholerae* serotype O1, a gram-negative, flagellated bacterium in the shape of a curved rod (vibrio). According to the CDC, cholera causes an estimated 3 to 5 million cases and 100,000 deaths each year.[4]

Because *V. cholerae* is killed by stomach acid, relatively large doses are needed for a few microbial cells to survive to reach the intestines and cause infection. The motile cells travel through the mucous layer of the intestines, where they attach to epithelial cells and release cholera enterotoxin. The toxin is an A-B toxin with activity through adenylate cyclase (see Virulence Factors of Bacterial and Viral Pathogens). Within the intestinal cell, cyclic AMP (cAMP) levels increase, which activates a chloride channel and results in the release of ions into the intestinal lumen. This increase in osmotic pressure in the lumen leads to water also entering the lumen. As the water and electrolytes leave the body, it causes rapid dehydration and electrolyte imbalance. Diarrhea is so profuse that it is often called "rice water stool," and patients are placed on cots with a hole in them to monitor the fluid loss (Figure 11.3.4).

Cholera is diagnosed by taking a stool sample and culturing for *Vibrio*. The bacteria are oxidase positive and show non-lactose fermentation on MacConkey agar. Gram-negative lactose fermenters will produce red colonies while non-fermenters will produce white/colorless colonies. Gram-positive bacteria will not grow on MacConkey. Lactose fermentation is commonly used for pathogen identification because the normal microbiota generally ferments lactose while pathogens do not. *V. cholerae* may also be cultured on thiosulfate citrate bile salts sucrose (TCBS) agar, a selective and differential media for *Vibrio* spp., which produce a distinct yellow colony.

Cholera may be self-limiting and treatment involves rehydration and electrolyte replenishment. Although antibiotics are not typically needed, they can be used for severe or disseminated disease. Tetracyclines are recommended, but doxycycline, erythromycin, orfloxacin, ciprofloxacin, and TMP/SMZ may be used. Recent evidence suggests that azithromycin is also a good first-line antibiotic. Good sanitation—including appropriate sewage treatment, clean supplies for cooking, and purified drinking water—is important to prevent infection (Figure 11.3.4)




Figure 11.3.4: (a) Outbreaks of cholera often occur in areas with poor sanitation or after natural disasters that compromise sanitation infrastructure. (b) At a cholera treatment center in Haiti, patients are receiving intravenous fluids to combat the dehydrating effects of this disease. They often lie on a cot with a hole in it and a bucket underneath to allow for monitoring of fluid loss. (c) This scanning electron micrograph shows *Vibrio cholera*. (credit a, b: modification of work by Centers for Disease Control and Prevention; credit c: modification of work by Janice Carr, Centers for Disease Control and Prevention)

*V. cholera* is not the only *Vibrio* species that can cause disease. *V. parahemolyticus* is associated with consumption of contaminated seafood and causes gastrointestinal illness with signs and symptoms such as watery diarrhea, nausea, fever, chills, and abdominal cramps. The bacteria produce a heat-stable hemolysin, leading to dysentery and possible disseminated disease. It also sometimes causes wound infections. *V. parahemolyticus* is diagnosed using cultures from blood, stool, or a wound. As with *V. cholera*, selective medium (especially TCBS agar) works well. Tetracycline and ciprofloxacin can be used to treat severe cases, but antibiotics generally are not needed.

*Vibrio vulnificus* is found in warm seawater and, unlike *V. cholerae*, is not associated with poor sanitary conditions. The bacteria can be found in raw seafood, and ingestion causes gastrointestinal illness. It can also be acquired by individuals with open skin wounds who are exposed to water with high concentrations of the pathogen. In some cases, the infection spreads to the

bloodstream and causes septicemia. Skin infection can lead to edema, ecchymosis (discoloration of skin due to bleeding), and abscesses. Patients with underlying disease have a high fatality rate of about 50%. It is of particular concern for individuals with chronic liver disease or who are otherwise immunodeficient because a healthy immune system can often prevent infection from developing. *V. vulnificus* is diagnosed by culturing for the pathogen from stool samples, blood samples, or skin abscesses. Adult patients are treated with doxycycline combined with a third generation cephalosporin or with fluoroquinolones, and children are treated with TMP/SMZ.

Two other vibrios, *Aeromonas hydrophila* and *Plesiomonas shigelloides*, are also associated with marine environments and raw seafood; they can also cause gastroenteritis. Like *V. vulnificus*, *A. hydrophila* is more often associated with infections in wounds, generally those acquired in water. In some cases, it can also cause septicemia. Other species of *Aeromonas* can cause illness. *P. shigelloides* is sometimes associated with more serious systemic infections if ingested in contaminated food or water. Culture can be used to diagnose *A. hydrophila* and *P. shigelloides* infections, for which antibiotic therapy is generally not needed. When necessary, tetracycline and ciprofloxacin, among other antibiotics, may be used for treatment of *A. hydrophila*, and fluoroquinolones and trimethoprim are the effective treatments for *P. shigelloides*.

**Exercise 11.3.5**

How does *V. cholera* infection cause rapid dehydration?

## Campylobacter jejuni Gastroenteritis

*Campylobacter* is a genus of gram-negative, spiral or curved bacteria. They may have one or two flagella. *Campylobacter jejuni* gastroenteritis, a form of campylobacteriosis, is a widespread illness that is caused by *Campylobacter jejuni*. The primary route of transmission is through poultry that becomes contaminated during slaughter. Handling of the raw chicken in turn contaminates cooking surfaces, utensils, and other foods. Unpasteurized milk or contaminated water are also potential vehicles of transmission. In most cases, the illness is self-limiting and includes fever, diarrhea, cramps, vomiting, and sometimes dysentery. More serious signs and symptoms, such as bacteremia, meningitis, pancreatitis, cholecystitis, and hepatitis, sometimes occur. It has also been associated with autoimmune conditions such as Guillain-Barré syndrome, a neurological disease that occurs after some infections and results in temporary paralysis. HUS following infection can also occur. The virulence in many strains is the result of hemolysin production and the presence of *Campylobacter* cytolethal distending toxin (CDT), a powerful deoxyribonuclease (DNase) that irreversibly damages host cell DNA.

Diagnosis involves culture under special conditions, such as elevated temperature, low oxygen tension, and often medium supplemented with antimicrobial agents. These bacteria should be cultured on selective medium (such as Campy CV, charcoal selective medium, or cefaperazone charcoal deoxycholate agar) and incubated under microaerophilic conditions for at least 72 hours at 42 °C. Antibiotic treatment is not usually needed, but erythromycin or ciprofloxacin may be used.

## Peptic Ulcers

The gram-negative bacterium *Helicobacter pylori* is able to tolerate the acidic environment of the human stomach and has been shown to be a major cause of peptic ulcers, which are ulcers of the stomach or duodenum. The bacterium is also associated with increased risk of stomach cancer (Figure 11.3.5). According to the CDC, approximately two-thirds of the population is infected with *H. pylori,* but less than 20% have a risk of developing ulcers or stomach cancer. *H. pylori* is found in approximately 80% of stomach ulcers and in over 90% of duodenal ulcers.[5]

*H. pylori* colonizes epithelial cells in the stomach using pili for adhesion. These bacteria produce urease, which stimulates an immune response and creates ammonia that neutralizes stomach acids to provide a more hospitable microenvironment. The infection damages the cells of the stomach lining, including those that normally produce the protective mucus that serves as a barrier between the tissue and stomach acid. As a result, inflammation (gastritis) occurs and ulcers may slowly develop. Ulcer formation can also be caused by toxin activity. It has been reported that 50% of clinical isolates of *H. pylori* have detectable levels of exotoxin activity *in vitro*.[6] This toxin, VacA, induces vacuole formation in host cells. VacA has no primary sequence homology with other bacterial toxins, and in a mouse model, there is a correlation between the presence of the toxin gene, the activity of the toxin, and gastric epithelial tissue damage.

Signs and symptoms include nausea, lack of appetite, bloating, burping, and weight loss. Bleeding ulcers may produce dark stools.

If no treatment is provided, the ulcers can become deeper, more tissues can be involved, and stomach perforation can occur. Because perforation allows digestive enzymes and acid to leak into the body, it is a very serious condition.

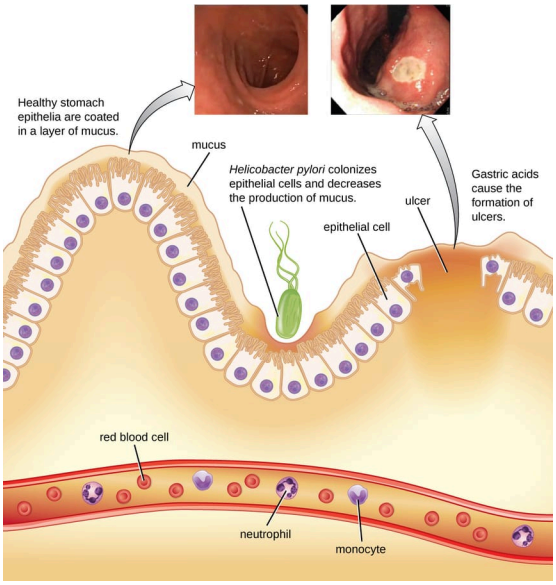



Figure 11.3.5: Helicobacter infection decreases mucus production and causes peptic ulcers. (credit top left photo: modification of work by "Santhosh Thomas"/YouTube; credit top right photo: modification of work by Moriya M, Uehara A, Okumura T, Miyamoto M, and Kohgo Y)

To diagnose *H. pylori* infection, multiple methods are available. In a breath test, the patient swallows radiolabeled urea. If *H. pylori* is present, the bacteria will produce urease to break down the urea. This reaction produces radiolabeled carbon dioxide that can be detected in the patient's breath. Blood testing can also be used to detect antibodies to *H. pylori*. The bacteria themselves can be detected using either a stool test or a stomach wall biopsy.

Antibiotics can be used to treat the infection. However, unique to *H. pylori,* the recommendation from the US Food and Drug Administration is to use a triple therapy. The current protocols are 10 days of treatment with omeprazole, amoxicillin, and clarithromycin (OAC); 14 days of treatment with bismuth subsalicylate, metronidazole, and tetracycline (BMT); or 10 or 14 days of treatment with lansoprazole, amoxicillin, and clarithromycin (LAC). Omeprazole, bismuth subsalicylate, and lansoprazole are not antibiotics but are instead used to decrease acid levels because *H. pylori* prefers acidic environments.

Although treatment is often valuable, there are also risks to *H. pylori* eradication. Infection with *H. pylori* may actually protect against some cancers, such as esophageal adenocarcinoma and gastroesophageal reflux disease.[78]

**Exercise 11.3.6**

How does *H. pylori* cause peptic ulcers?

## Clostridium perfringens Gastroenteritis

*Clostridium perfringens* gastroenteritis is a generally mild foodborne disease that is associated with undercooked meats and other foods. *C. perfringens* is a gram-positive, rod-shaped, endospore-forming anaerobic bacterium that is tolerant of high and low temperatures. At high temperatures, the bacteria can form endospores that will germinate rapidly in foods or within the intestine. Food poisoning by type A strains is common. This strain always produces an enterotoxin, sometimes also present in other strains, that causes the clinical symptoms of cramps and diarrhea. A more severe form of the illness, called pig-bel or enteritis necroticans, causes hemorrhaging, pain, vomiting, and bloating. Gangrene of the intestines may result. This form has a high mortality rate but is rare in the United States.

Diagnosis involves detecting the *C. perfringens* toxin in stool samples using either molecular biology techniques (PCR detection of the toxin gene) or immunology techniques (ELISA). The bacteria itself may also be detected in foods or in fecal samples. Treatment includes rehydration therapy, electrolyte replacement, and intravenous fluids. Antibiotics are not recommended

because they can damage the balance of the microbiota in the gut, and there are concerns about antibiotic resistance. The illness can be prevented through proper handling and cooking of foods, including prompt refrigeration at sufficiently low temperatures and cooking food to a sufficiently high temperature.

## Clostridium difficile

*Clostridium difficile* is a gram-positive rod that can be a commensal bacterium as part of the normal microbiota of healthy individuals. When the normal microbiota is disrupted by long-term antibiotic use, it can allow the overgrowth of this bacterium, resulting in antibiotic-associated diarrhea caused by *C. difficile*. Antibiotic-associated diarrhea can also be considered a nosocomial disease. Patients at the greatest risk of *C. difficile* infection are those who are immunocompromised, have been in health-care settings for extended periods, are older, have recently taken antibiotics, have had gastrointestinal procedures done, or use proton pump inhibitors, which reduce stomach acidity and allow proliferation of *C. difficile*. Because this species can form endospores, it can survive for extended periods of time in the environment under harsh conditions and is a considerable concern in health-care settings.

This bacterium produces two toxins, *Clostridium difficile* toxin A (TcdA) and *Clostridium difficile* toxin B (TcdB). These toxins inactivate small GTP-binding proteins, resulting in actin condensation and cell rounding, followed by cell death. Infections begin with focal necrosis, then ulceration with exudate, and can progress to pseudomembranous colitis, which involves inflammation of the colon and the development of a pseudomembrane of fibrin containing dead epithelial cells and leukocytes (Figure 11.3.6 ). Watery diarrhea, dehydration, fever, loss of appetite, and abdominal pain can result. Perforation of the colon can occur, leading to septicemia, shock, and death. *C. difficile* is also associated with necrotizing enterocolitis in premature babies and neutropenic enterocolitis associated with cancer therapies.

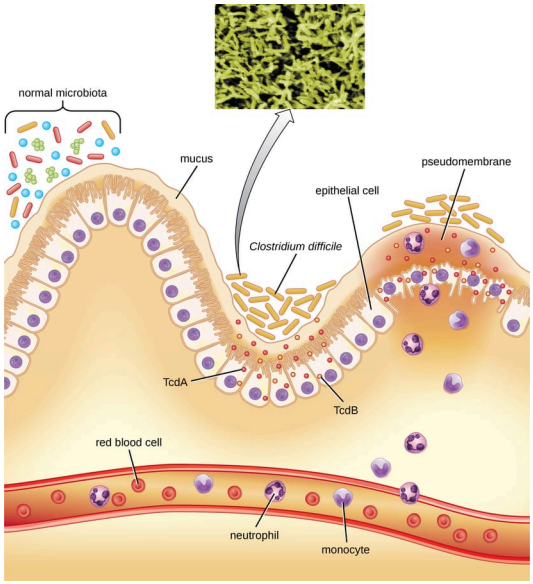



Figure 11.3.6: Clostridium difficile is able to colonize the mucous membrane of the colon when the normal microbiota is disrupted. The toxins TcdA and TcdB trigger an immune response, with neutrophils and monocytes migrating from the bloodstream to the site of infection. Over time, inflammation and dead cells contribute to the development of a pseudomembrane. (credit micrograph: modification of work by Janice Carr, Centers for Disease Control and Prevention)

Diagnosis is made by considering the patient history (such as exposure to antibiotics), clinical presentation, imaging, endoscopy, lab tests, and other available data. Detecting the toxin in stool samples is used to confirm diagnosis. Although culture is preferred, it is rarely practical in clinical practice because the bacterium is an obligate anaerobe. Nucleic acid amplification tests, including PCR, are considered preferable to ELISA testing for molecular analysis.

The first step of conventional treatment is to stop antibiotic use, and then to provide supportive therapy with electrolyte replacement and fluids. Metronidazole is the preferred treatment if the *C. difficile* diagnosis has been confirmed. Vancomycin can also be used, but it should be reserved for patients for whom metronidazole was ineffective or who meet other criteria (e.g., under 10 years of age, pregnant, or allergic to metronidazole).

A newer approach to treatment, known as a fecal transplant, focuses on restoring the microbiota of the gut in order to combat

the infection. In this procedure, a healthy individual donates a stool sample, which is mixed with saline and transplanted to the recipient via colonoscopy, endoscopy, sigmoidoscopy, or enema. It has been reported that this procedure has greater than 90% success in resolving *C. difficile* infections.[9]

**Exercise 11.3.7**

How does antibiotic use lead to *C. difficile* infections?

## Foodborne Illness Due to *Bacillus cereus*

*Bacillus cereus*, commonly found in soil, is a gram-positive endospore-forming bacterium that can sometimes cause foodborne illness. *B. cereus* endospores can survive cooking and produce enterotoxins in food after it has been heated; illnesses often occur after eating rice and other prepared foods left at room temperature for too long. The signs and symptoms appear within a few hours of ingestion and include nausea, pain, and abdominal cramps. *B. cereus* produces two toxins: one causing diarrhea, and the other causing vomiting. More severe signs and symptoms can sometimes develop.

Diagnosis can be accomplished by isolating bacteria from stool samples or vomitus and uneaten infected food. Treatment involves rehydration and supportive therapy. Antibiotics are not typically needed, as the illness is usually relatively mild and is due to toxin activity.

## Foodborne Illness Due to *Yersinia*

The genus *Yersinia* is best known for *Yersinia pestis*, a gram-negative rod that causes the plague. However, *Y. enterocolitica* and *Y. pseudotuberculosis* can cause gastroenteritis. The infection is generally transmitted through the fecal-oral route, with ingestion of food or water that has been contaminated by feces. Intoxication can also result because of the activity of its endotoxin and exotoxins (enterotoxin and cytotoxin necrotizing factor). The illness is normally relatively mild and self-limiting. However, severe diarrhea and dysentery can develop in infants. In adults, the infection can spread and cause complications such as reactive arthritis, thyroid disorders, endocarditis, glomerulonephritis, eye inflammation, and/or erythema nodosum. Bacteremia may develop in rare cases.

Diagnosis is generally made by detecting the bacteria in stool samples. Samples may also be obtained from other tissues or body fluids. Treatment is usually supportive, including rehydration, without antibiotics. If bacteremia or other systemic disease is present, then antibiotics such as fluoroquinolones, aminoglycosides, doxycycline, and trimethoprim-sulfamethoxazole may be used. Recovery can take up to two weeks.

**Exercise 11.3.8**

Compare and contrast foodborne illnesses due to *B. cereus* and *Yersinia*.

**Bacterial Infections of the Gastrointestinal Tract**

Bacterial infections of the gastrointestinal tract generally occur when bacteria or bacterial toxins are ingested in contaminated food or water. Toxins and other virulence factors can produce gastrointestinal inflammation and general symptoms such as diarrhea and vomiting. Bacterial GI infections can vary widely in terms of severity and treatment. Some can be treated with antibiotics, but in other cases antibiotics may be ineffective in combating toxins or even counterproductive if they compromise the GI microbiota. Figure 11.3.7 and Figure 11.3.8 the key features of common bacterial GI infections.

| Bacterial Infections of the GI Tract | | | | | |
|---|---|---|---|---|---|
| **Disease** | **Pathogen** | **Signs and Symptoms** | **Transmission** | **Diagnostic Tests** | **Antimicrobial Drugs** |
| *Bacillus cereus* infection | *Bacillus cereus* | Nausea, pain, abdominal cramps, diarrhea, or vomiting | Ingestion of contaminated rice or meat, even after cooking | Testing stool sample, vomitus, or uneaten food for presence of bacteria | None |
| *Campylobacter jejuni* gastroenteritis | *Campylobacter jejuni* | Fever, diarrhea, cramps, vomiting, and sometimes dysentery; sometimes more severe organ or autoimmune effects | Ingestion of unpasteurized milk, under-cooked chicken, or contaminated water | Culture on selective medium with elevated temperature and low oxygen concentration | Generally none; erythromycin or ciprofloxacin if necessary |
| Cholera | *Vibrio cholerae* | Severe diarrhea and fluid loss, potentially leading to shock, renal failure, and death | Ingestion of contaminated water or food | Culture on selective medium (TCBS agar); distinguished as oxidase positive with fermentative metabolisms | Generally none; tetracyclines, azithromycin, others if necessary |
| *Clostridium difficile* infection | *Clostridium difficile* | Pseudomem-branous colitis, watery diarrhea, fever, abdominal pain, loss of appe-tite, dehydration; in severe cases, perforation of the colon, septicemia, shock, and death | Overgrowth of *C. difficile* in the normal microbiota due to antibiotic use; hospital-acquired infections in immunocompro-mised patients | Detection of toxin in stool, nucleic acid amplification tests (e.g., PCR) | Discontinuation of previous antibiotic treatment; metronidazole or vancomycin |
| *Clostridium perfringens* gastroenteritis | *Clostridium perfringens* (especially type A) | Mild cramps and diarrhea in most cases; in rare cases, hemor-rhaging, vomiting, intestinal gangrene, and death | Ingestion of undercooked meats containing *C. perfringens* endospores | Detection of toxin or bacteria in stool or uneaten food | None |
| *E. coli* infection | ETEC, EPEC, EIEC, EHEC | Watery diarrhea, dysentery, cramps, malaise, fever, chills, dehydration; in EHEC, possible severe compli-cations such as hematolytic uremic syndrome | Ingestion of contaminated food or water | Tissue culture, immunochemi-cal assays, PCR, gene probes | Not recommended for EIEC and EHEC; fluoroquinolones, doxycycline, rifaximin, and TMP/SMZ possible for ETEC and EPEC |

Figure 11.3.7: Bacterial infections of the GI tract.

| Bacterial Infections of the GI Tract (continued) | | | | | |
|---|---|---|---|---|---|
| **Disease** | **Pathogen** | **Signs and Symptoms** | **Transmission** | **Diagnostic Tests** | **Antimicrobial Drugs** |
| Peptic ulcers | *Helicobacter pylori* | Nausea, bloating, burping, lack of appetite, weight loss, perforation of stomach, blood in stools | Normal flora, can also be acquired via saliva; fecal-oral route via contaminated food and water | Breath test, detection of antibodies in blood, detection of bacteria in stool sample or stomach biopsy | Amoxicillin, clarithromycin metronidazole, tetracycline, lansoprazole; antacids may also be given in combination with antibiotics |
| Salmonellosis | *Salmonella enterica*, serotype Enteritides | Fever, nausea, vomiting, abdominal cramps, headache, diarrhea; can be fatal in infants | Ingestion of contaminated food, handling of eggshells or contaminated animals | Culturing, serotyping and DNA fingerprinting | Not generally recommended; fluoroquinolones, ampicillin, others for immunocompromised patients |
| *Shigella* dysentery | *Shigella dysenteriae*, *S. flexneri*, *S. boydii*, and *S. sonnei* | Abdominal cramps, fever, diarrhea, dysentery; possible complications: reactive arthritis and hemolytic uremic syndrome | Fecal-oral route via contaminated food and water | Testing of stool samples for presence of blood and leukocytes; culturing, PCR, immunoassay for *S. dysenteriae* | Ciprofloxacin, azithromycin |
| Staphylococcal food poisoning | *Staphylococcus aureus* | Rapid-onset nausea, diarrhea, vomiting lasting 24–48 hours; possible dehydration and change in blood pressure and heart rate | Ingestion of raw or undercooked meat or dairy products conta-minated with staphylococcal enterotoxins | ELISA to detect enterotoxins in uneaten food, stool, or vomitus | None |
| Typhoid fever | *S. entrica*, subtypes Typhi or Paratyphi | Aches, headaches, nausea, lethargy, diarrhea or constipation, possible rash; lethal perforation of intestine can occur | Fecal-oral route; may be spread by asymptomatic carriers | Culture of blood, stool, or bone marrow, serologic tests; PCR tests when available | Fluoroquinolones, ceftriaxone, azithromycin; preventive vaccine available |
| *Yersinia* infection | *Yersinia enterocolitica*, *Y. pseudo-tuberculosis* | Generally mild diarrhea and abdominal cramps; in some cases, bacteremia can occur, leading to severe complications | Fecal-oral route, typically via contaminated food or water | Testing stool samples, tissues, body fluids | Generally none; fluoroquinolones, aminoglycosides, others for systemic infections |

Figure 11.3.8: Bacterial infections of the GI tract (continued).

## Clinical Focus: Part 2

At the hospital, Carli's doctor began to think about possible causes of her severe gastrointestinal distress. One possibility was food poisoning, but no one else in her family was sick. The doctor asked about what Carli had eaten the previous day; her mother mentioned that she'd had eggs for lunch, and that they may have been a little undercooked. The doctor took a sample of Carli's stool and sent it for laboratory testing as part of her workup. She suspected that Carli could have a case of bacterial or viral gastroenteritis, but she needed to know the cause in order to prescribe an appropriate treatment.

In the laboratory, technicians microscopically identified gram-negative bacilli in Carli's stool sample. They also established a pure culture of the bacteria and analyzed it for antigens. This testing showed that the causative agent was *Salmonella*.

### Exercise 11.3.9

What should the doctor do now to treat Carli?

## Key Concepts and Summary

- Major causes of gastrointestinal illness include *Salmonella* spp., *Staphylococcus* spp., *Helicobacter pylori*, *Clostridium perfringens*, *Clostridium difficile*, *Bacillus cereus*, and *Yersinia* bacteria.
- *C. difficile* is an important cause of hospital acquired infection.
- *Vibrio cholerae* causes **cholera**, which can be a severe diarrheal illness.
- Different strains of *E. coli*, including **ETEC**, **EPEC**, **EIEC**, and **EHEC**, cause different illnesses with varying degrees of severity.
- *H. pylori* is associated with **peptic ulcers**.
- *Salmonella enterica* serotypes can cause **typhoid fever**, a more severe illness than **salmonellosis**.
- Rehydration and other supportive therapies are often used as general treatments.
- Careful antibiotic use is required to reduce the risk of causing *C. difficile* infections and when treating antibiotic-resistant infections.

## Footnotes

1. 1 Jaya Sureshbabu. “Shigella Infection Workup.” *Medscape*. Updated Jun 28, 2016. http://emedicine.medscape.com/article/968773-workup.
2. 2 Centers for Disease Control and Prevention. *Salmonella*. Updated August 25, 2016. https://www.cdc.gov/salmonella.
3. 3 Kaci Hickox. “Stop Calling Me the ‘Ebola Nurse.’” *The Guardian*. November 17, 2014. www.theguardian.com/commentis...se-kaci-hickox.
4. 4 Centers for Disease Control and Prevention. *Cholera—Vibrio cholerae Infection*. Updated November 6, 2014. http://www.cdc.gov/cholera/general. Accessed Sept 14, 2016.
5. 5 Centers for Disease Control and Prevention. “*Helicobacter pylori*: Fact Sheet for Health Care Providers.” Updated July 1998. www.cdc.gov/ulcer/files/hpfacts.pdf.
6. 6 T. L. Cover. “The Vacuolating Cytotoxin of *Helicobacter pylori*.” *Molecular Microbiology* 20 (1996) 2: pp. 241–246. http://www.ncbi.nlm.nih.gov/pubmed/8733223.
7. 7 Martin J. Blaser. “Disappearing Microbiota: *Helicobacter pylori* Protection against Esophageal Adenocarcinoma.” *Cancer Prevention Research* 1 (2008) 5: pp. 308–311. http://cancerpreventionresearch.aacr....full.pdf+html.
8. 8 Ivan F. N. Hung and Benjamin C. Y. Wong. “Assessing the Risks and Benefits of Treating *Helicobacter pylori* Infection.” *Therapeutic Advances in Gastroenterology* 2 (2009) 3: pp, 141–147. doi: 10.1177/1756283X08100279.
9. 9 Faith Rohlke and Neil Stollman. “Fecal Microbiota Transplantation in Relapsing *Clostridium difficile* Infection,” *Therapeutic Advances in Gastroenterology* 5 (2012) 6: 403–420. doi: 10.1177/1756283X12453637.

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# 11.4: Viral Infections of the Gastrointestinal Tract

**Learning Objectives**

- Identify the most common viruses that can cause infections of the GI tract
- Compare the major characteristics of specific viral diseases affecting the GI tract and liver

In the developing world, acute viral gastroenteritis is devastating and a leading cause of death for children.[1] Worldwide, diarrhea is the second leading cause of mortality for children under age five, and 70% of childhood gastroenteritis is viral.[2] As discussed, there are a number of bacteria responsible for diarrhea, but viruses can also cause diarrhea. *E. coli* and rotavirus are the most common causative agents in the developing world. In this section, we will discuss rotaviruses and other, less common viruses that can also cause gastrointestinal illnesses.

## Gastroenteritis Caused by Rotaviruses

Rotaviruses are double-stranded RNA viruses in the family Reoviridae. They are responsible for common diarrheal illness, although prevention through vaccination is becoming more common. The virus is primarily spread by the fecal-oral route (Figure 11.4.1).

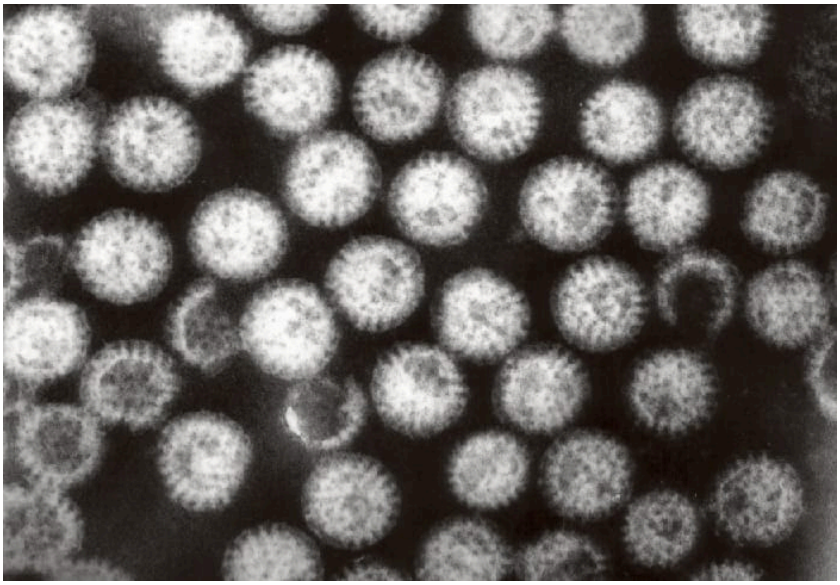


Figure 11.4.1: Rotaviruses in a fecal sample are visualized using electron microscopy. (credit: Dr. Graham Beards)

These viruses are widespread in children, especially in day-care centers. The CDC estimates that 95% of children in the United States have had at least one rotavirus infection by the time they reach age five.[3] Due to the memory of the body's immune system, adults who come into contact with rotavirus will not contract the infection or, if they do, are asymptomatic. The elderly, however, are vulnerable to rotavirus infection due to weakening of the immune system with age, so infections can spread through nursing homes and similar facilities. In these cases, the infection may be transmitted from a family member who may have subclinical or clinical disease. The virus can also be transmitted from contaminated surfaces, on which it can survive for some time.

Infected individuals exhibit fever, vomiting, and diarrhea. The virus can survive in the stomach following a meal, but is normally found in the small intestines, particularly the epithelial cells on the villi. Infection can cause food intolerance, especially with respect to lactose. The illness generally appears after an incubation period of about two days and lasts for approximately one week (three to eight days). Without supportive treatment, the illness can cause severe fluid loss, dehydration, and even death. Even with milder illness, repeated infections can potentially lead to malnutrition, especially in developing countries, where rotavirus infection is common due to poor sanitation and lack of access to clean drinking water. Patients (especially children) who are malnourished after an episode of diarrhea are more susceptible to future diarrheal illness, increasing their risk of death from

rotavirus infection.

The most common clinical tool for diagnosis is enzyme immunoassay, which detects the virus from fecal samples. Latex agglutination assays are also used. Additionally, the virus can be detected using electron microscopy and RT-PCR.

Treatment is supportive with oral rehydration therapy. Preventive vaccination is also available. In the United States, rotavirus vaccines are part of the standard vaccine schedule and administration follows the guidelines of the World Health Organization (WHO). The WHO recommends that all infants worldwide receive the rotavirus vaccine, the first dose between six and 15 weeks of age and the second before 32 weeks.[4]

## Gastroenteritis Caused by Noroviruses

Noroviruses, commonly identified as Norwalk viruses, are caliciviruses. Several strains can cause gastroenteritis. There are millions of cases a year, predominately in infants, young children, and the elderly. These viruses are easily transmitted and highly contagious. They are known for causing widespread infections in groups of people in confined spaces, such as on cruise ships. The viruses can be transmitted through direct contact, through touching contaminated surfaces, and through contaminated food. Because the virus is not killed by disinfectants used at standard concentrations for killing bacteria, the risk of transmission remains high, even after cleaning.

The signs and symptoms of norovirus infection are similar to those for rotavirus, with watery diarrhea, mild cramps, and fever. Additionally, these viruses sometimes cause projectile vomiting. The illness is usually relatively mild, develops 12 to 48 hours after exposure, and clears within a couple of days without treatment. However, dehydration may occur.

Norovirus can be detected using PCR or enzyme immunoassay (EIA) testing. RT-qPCR is the preferred approach as EIA is insufficiently sensitive. If EIA is used for rapid testing, diagnosis should be confirmed using PCR. No medications are available, but the illness is usually self-limiting. Rehydration therapy and electrolyte replacement may be used. Good hygiene, hand washing, and careful food preparation reduce the risk of infection.

## Gastroenteritis Caused by Astroviruses

Astroviruses are single-stranded RNA viruses (family Astroviridae) that can cause severe gastroenteritis, especially in infants and children. Signs and symptoms include diarrhea, nausea, vomiting, fever, abdominal pain, headache, and malaise. The viruses are transmitted through the fecal-oral route (contaminated food or water). For diagnosis, stool samples are analyzed. Testing may involve enzyme immunoassays and immune electron microscopy. Treatment involves supportive rehydration and electrolyte replacement if needed.

### Exercise 11.4.1

Why are rotaviruses, noroviruses, and astroviruses more common in children?

### Viral Infections of the Gastrointestinal Tract

A number of viruses can cause gastroenteritis, characterized by inflammation of the GI tract and other signs and symptoms with a range of severities. As with bacterial GI infections, some cases can be relatively mild and self-limiting, while others can become serious and require intensive treatment. Antimicrobial drugs are generally not used to treat viral gastroenteritis; generally, these illnesses can be treated effectively with rehydration therapy to replace fluids lost in bouts of diarrhea and vomiting. Because most viral causes of gastroenteritis are quite contagious, the best preventive measures involve avoiding and/or isolating infected individuals and limiting transmission through good hygiene and sanitation.

| Viral Causes of Gastroenteritis | | | | | |
|---|---|---|---|---|---|
| **Disease** | **Pathogen** | **Signs and Symptoms** | **Transmission** | **Diagnostic Tests** | **Vaccine** |
| Astrovirus gastroenteritis | Astroviru-ses | Fever, headache, abdominal pain, malaise, diarrhea, vomiting | Fecal-oral route, contaminated food or water | Enzyme immunoassays, immune electron microscopy | None |
| Norovirus gastroenteritis | Noroviruses | Fever, diarrhea, projectile vomiting, dehydration; generally self-limiting within two days | Highly contagious via direct contact or contact with contaminated food or fomites | Rapid enzyme immunoassay confirmed with RT-qPCR | None |
| Rotavirus gastroenteritis | Rotaviruses | Fever, diarrhea, vomiting, severe dehydration; recurring infections can lead to malnutrition and death | Fecal-oral route; children and elderly most susceptible | Enzyme immunoassay of stool sample, latex agglutination assays, RT-PCR | Preventive vaccine recommended for infants |

Figure 11.4.2: Viral causes of Gastroenteritis.

## Hepatitis

Hepatitis is a general term meaning inflammation of the liver, which can have a variety of causes. In some cases, the cause is viral infection. There are five main hepatitis viruses that are clinically significant: hepatitisviruses A (HAV), B (HBV), C (HCV), D, (HDV) and E (HEV) (Figure 11.4.3). Note that other viruses, such as Epstein-Barr virus (EBV), yellow fever, and cytomegalovirus (CMV) can also cause hepatitis and are discussed in Viral Infections of the Circulatory and Lymphatic Systems.

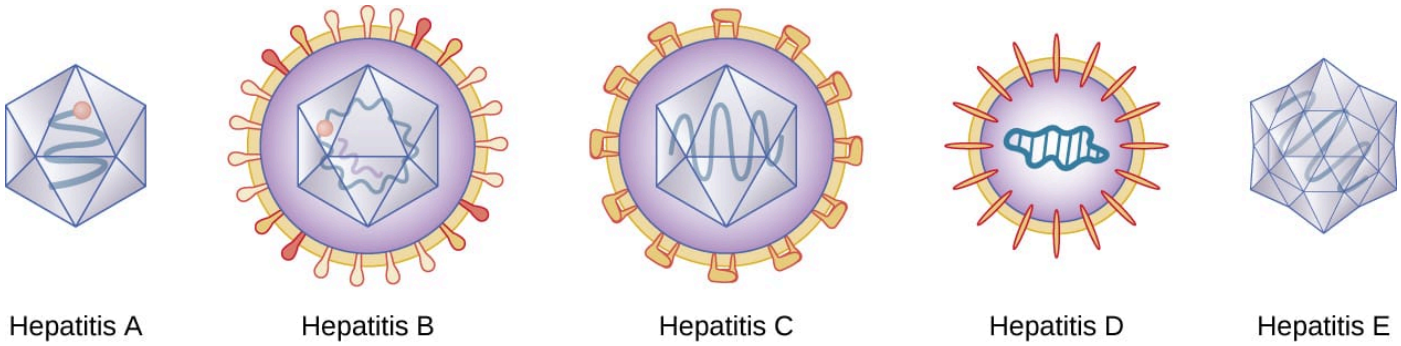



Figure 11.4.3: Five main types of viruses cause hepatitis. HAV is a non-enveloped ssRNA(+) virus and is a member of the picornavirus family (Baltimore Group IV). HBV is a dsDNA enveloped virus, replicates using reverse transcriptase, and is a member of the hepadnavirus family (Baltimore Group VII). HCV is an enveloped ssRNA(+) virus and is a member of the flavivirus family (Baltimore Group IV). HDV is an enveloped ssRNA(–) that is circular (Baltimore Group V). This virus can only propagate in the presence of HBV. HEV is a non-enveloped ssRNA(+) virus and a member of the hepeviridae family (Baltimore Group IV).

Although the five hepatitis viruses differ, they can cause some similar signs and symptoms because they all have an affinity for hepatocytes (liver cells). HAV and HEV can be contracted through ingestion while HBV, HCV, and HDV are transmitted by parenteral contact. It is possible for individuals to become long term or chronic carriers of hepatitis viruses.

The virus enters the blood (viremia), spreading to the spleen, the kidneys, and the liver. During viral replication, the virus infects hepatocytes. The inflammation is caused by the hepatocytes replicating and releasing more hepatitis virus. Signs and symptoms include malaise, anorexia, loss of appetite, dark urine, pain in the upper right quadrant of the abdomen, vomiting, nausea, diarrhea, joint pain, and gray stool. Additionally, when the liver is diseased or injured, it is unable to break down hemoglobin effectively, and bilirubin can build up in the body, giving the skin and mucous membranes a yellowish color, a condition called jaundice (Figure 11.4.4). In severe cases, death from liver necrosis may occur.




Figure 11.4.4: (a) Hepatitis is inflammation of the liver resulting from a variety of root causes. It can cause jaundice. (b) Jaundice is characterized by yellowing of the skin, mucous membranes, and sclera of the eyes. (credit b left: modification of work by James Heilman, MD; credit b right: modification of work by "Sab3el3eish"/Wikimedia Commons)

Despite having many similarities, each of the hepatitis viruses has its own unique characteristics. HAV is generally transmitted through the fecal-oral route, close personal contact, or exposure to contaminated water or food. Hepatitis A can develop after an incubation period of 15 to 50 days (the mean is 30). It is normally mild or even asymptomatic and is usually self-limiting within weeks to months. A more severe form, fulminant hepatitis, rarely occurs but has a high fatality rate of 70–80%. Vaccination is available and is recommended especially for children (between ages one and two), those traveling to countries with higher risk, those with liver disease and certain other conditions, and drug users.

Although HBV is associated with similar signs and symptoms, transmission and outcomes differ. This virus has a mean incubation period of 120 days and is generally associated with exposure to infectious blood or body fluids such as semen or saliva. Exposure can occur through skin puncture, across the placenta, or through mucosal contact, but it is not spread through casual contact such as hugging, hand holding, sneezing, or coughing, or even through breastfeeding or kissing. Risk of infection is greatest for those who use intravenous drugs or who have sexual contact with an infected individual. Health-care workers are also at risk from needle sticks and other injuries when treating infected patients. The infection can become chronic and may progress to cirrhosis or liver failure. It is also associated with liver cancer. Chronic infections are associated with the highest mortality rates and are more common in infants. Approximately 90% of infected infants become chronic carriers, compared with only 6–10% of infected adults.[5] Vaccination is available and is recommended for children as part of the standard vaccination schedule (one dose at birth and the second by 18 months of age) and for adults at greater risk (e.g., those with certain diseases, intravenous drug users, and those who have sex with multiple partners). Health-care agencies are required to offer the HBV vaccine to all workers who have occupational exposure to blood and/or other infectious materials.

HCV is often undiagnosed and therefore may be more widespread than is documented. It has a mean incubation period of 45 days and is transmitted through contact with infected blood. Although some cases are asymptomatic and/or resolve spontaneously, 75%–85% of infected individuals become chronic carriers. Nearly all cases result from parenteral transmission often associated with IV drug use or transfusions. The risk is greatest for individuals with past or current history of intravenous drug use or who have had sexual contact with infected individuals. It has also been spread through contaminated blood products and can even be transmitted through contaminated personal products such as toothbrushes and razors. New medications have recently been developed that show great effectiveness in treating HCV and that are tailored to the specific genotype causing the infection.

HDV is uncommon in the United States and only occurs in individuals who are already infected with HBV, which it requires for replication. Therefore, vaccination against HBV is also protective against HDV infection. HDV is transmitted through contact with infected blood.

HEV infections are also rare in the United States but many individuals have a positive antibody titer for HEV. The virus is most commonly spread by the fecal-oral route through food and/or water contamination, or person-to-person contact, depending on the genotype of the virus, which varies by location. There are four genotypes that differ somewhat in their mode of transmission, distribution, and other factors (for example, two are zoonotic and two are not, and only one causes chronic infection). Genotypes

three and four are only transmitted through food, while genotypes one and two are also transmitted through water and fecal-oral routes. Genotype one is the only type transmitted person-to-person and is the most common cause of HEV outbreaks. Consumption of undercooked meat, especially deer or pork, and shellfish can lead to infection. Genotypes three and four are zoonoses, so they can be transmitted from infected animals that are consumed. Pregnant women are at particular risk. This disease is usually self-limiting within two weeks and does not appear to cause chronic infection.

General laboratory testing for hepatitis begins with blood testing to examine liver function (Figure 11.4.5). When the liver is not functioning normally, the blood will contain elevated levels of alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), direct bilirubin, total bilirubin, serum albumin, serum total protein, and calculated globulin, albumin/globulin (A/G) ratio. Some of these are included in a complete metabolic panel (CMP), which may first suggest a possible liver problem and indicate the need for more comprehensive testing. A hepatitis virus serological test panel can be used to detect antibodies for hepatitis viruses A, B, C, and sometimes D. Additionally, other immunological and genomic tests are available.

Specific treatments other than supportive therapy, rest, and fluids are often not available for hepatitis virus infection, except for HCV, which is often self-limited. Immunoglobulins can be used prophylactically following possible exposure. Medications are also used, including interferon alpha 2b and antivirals (e.g., lamivudine, entecavir, adefovir, and telbivudine) for chronic infections. Hepatitis C can be treated with interferon (as monotherapy or combined with other treatments), protease inhibitors, and other antivirals (e.g., the polymerase inhibitor sofosbuvir). Combination treatments are commonly used. Antiviral and immunosuppressive medications may be used for chronic cases of HEV. In severe cases, liver transplants may be necessary. Additionally, vaccines are available to prevent infection with HAV and HBV. The HAV vaccine is also protective against HEV. The HBV vaccine is also protective against HDV. There is no vaccine against HCV.

### Link to Learning

Learn more information about hepatitis virus infections.

### Exercise 11.4.2

Why do the five different hepatitis viruses all cause similar signs and symptoms?

### Preventing HBV Transmission in Health-Care Settings

Hepatitis B was once a leading on-the-job hazard for health-care workers. Many health-care workers over the years have become infected, some developing cirrhosis and liver cancer. In 1982, the CDC recommended that health-care workers be vaccinated against HBV, and rates of infection have declined since then. Even though vaccination is now common, it is not always effective and not all individuals are vaccinated. Therefore, there is still a small risk for infection, especially for health-care workers working with individuals who have chronic infections, such as drug addicts, and for those with higher risk of needle sticks, such as phlebotomists. Dentists are also at risk.

Health-care workers need to take appropriate precautions to prevent infection by HBV and other illnesses. Blood is the greatest risk, but other body fluids can also transmit infection. Damaged skin, as occurs with eczema or psoriasis, can also allow transmission. Avoiding contact with body fluids, especially blood, by wearing gloves and face protection and using disposable syringes and needles reduce the risk of infection. Washing exposed skin with soap and water is recommended. Antiseptics may also be used, but may not help. Post-exposure treatment, including treatment with hepatitis B immunoglobulin (HBIG) and vaccination, may be used in the event of exposure to the virus from an infected patient. Detailed protocols are available for managing these situations. The virus can remain infective for up to seven days when on surfaces, even if no blood or other fluids are visible, so it is important to consider the best choices for disinfecting and sterilizing equipment that could potentially transmit the virus. The CDC recommends a solution of 10% bleach to disinfect surfaces.[6] Finally, testing blood products is important to reduce the risk of transmission during transfusions and similar procedures.

## Viral Hepatitis

Hepatitis involves inflammation of the liver that typically manifests with signs and symptoms such as jaundice, nausea, vomiting, joint pain, gray stool, and loss of appetite. However, the severity and duration of the disease can vary greatly depending on the causative agent. Some infections may be completely asymptomatic, whereas others may be life threatening. The five different viruses capable of causing hepatitis are compared in Figure 11.4.5. For the sake of comparison, this table presents only the unique aspects of each form of viral hepatitis, not the commonalities.

**Viral Forms of Hepatitis**

| Disease | Pathogen | Signs and Symptoms | Transmission | Antimicrobial Drugs | Vaccine |
|---|---|---|---|---|---|
| Hepatitis A | Hepatitisvirus A (HAV) | Usually asymptomatic or mild and self-limiting within one to two weeks to a few months, sometimes longer but not, chronic; in rare cases leads to serious or fatal fulminant hepatitis | Contaminated food, water, objects, and person to person | None | Vaccine recommended for one year olds and high-risk adults |
| Hepatitis B | Hepatitisvirus B (HBV) | Similar to Hepatitis A, but may progress to cirrhosis and liver failure; associated with liver cancer | Contact with infected body fluids (blood, semen, saliva), e.g., via IV drug use, sexual transmission, health-care workers treating infected patients | Interferon, entecavir, tenofovir, lamivudine, adefovir | Vaccine recommended for infants and high-risk adults |
| Hepatitis C | Hepatitisvirus C (HCV) | Often asymptomatic, with 75%–85% chronic carriers; may progress to cirrhosis and liver failure; associated with liver cancer | Contact with infected body fluids, e.g., via IV drug use, transfusions, sexual transmission | Depends on geno-type and on whether cirrhosis is present; interferons, new treatment such as simeprevir plus sofosbuvir, ombitasvir/ paritaprevir/ritonavir and dasabuvir | None available |
| Hepatitis D | Hepatitisvirus D (HDV) | Similar to hepatitis B; usually self-limiting within one to two weeks but can become chronic or fulminant in rare cases | Contact with infected blood; infections can only occur in patients already infected with hepatitis B | None | Hepatitis B vaccine protects against HDV |
| Hepatitis E | Hepatitisvirus E (HEV) | Generally asymptomatic or mild and self-limiting; typically does not cause chronic disease | Fecal-oral route, often in contaminated water or undercooked meat; most common in developing countries | Supportive treatment; usually self-limiting, but some strains can become chronic; antiviral and immunosuppressive possible for chronic cases | Vaccine available in China only |

Figure 11.4.5: Viral forms of Hepatitis.

## Key Concepts and Summary

- Common viral causes of gastroenteritis include rotaviruses, noroviruses, and astroviruses.
- Hepatitis may be caused by several unrelated viruses: hepatitis viruses A, B, C, D, and E.
- The hepatitis viruses differ in their modes of transmission, treatment, and potential for chronic infection.

## Footnotes

1. 1 Caleb K. King, Roger Glass, Joseph S. Bresee, Christopher Duggan. “Managing Acute Gastroenteritis Among Children: Oral Rehydration, Maintenance, and Nutritional Therapy.” *MMWR* 52 (2003) RR16: pp. 1–16. http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5216a1.htm.
2. 2 Elizabeth Jane Elliott. “Acute Gastroenteritis in Children.” *British Medical Journal* 334 (2007) 7583: 35–40, doi: 10.1136/bmj.39036.406169.80; S. Ramani and G. Kang. “Viruses Causing Diarrhoea in the Developing World.” *Current Opinions in Infectious Diseases* 22 (2009) 5: pp. 477–482. doi: 10.1097/QCO.0b013e328330662f; Michael Vincent F Tablang. “Viral Gastroenteritis.” *Medscape*. http://emedicine.medscape.com/article/176515-overview.
3. 3 Centers for Disease Control and Prevention. “Rotavirus,” *The Pink Book*. Updated September 8, 2015. http://www.cdc.gov/vaccines/pubs/pinkbook/rota.html.
4. 4 World Health Organization. “Rotavirus.” *Immunization, Vaccines, and Biologicals*. Updated April 21, 2010. www.who.int/immunization/topics/rotavirus/en/.
5. 5 Centers for Disease Control and Prevention. “The ABCs of Hepatitis.” Updated 2016. http://www.cdc.gov/hepatitis/resourc...s/abctable.pdf.
6. 6 Centers for Disease Control and Prevention. “Hepatitis B FAQs for Health Professionals.” Updated August 4, 2016. http://www.cdc.gov/hepatitis/HBV/HBVfaq.htm.

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# 11.5: Protozoan Infections of the Gastrointestinal Tract

**Learning Objectives**

- Identify the most common protozoans that can cause infections of the GI tract
- Compare the major characteristics of specific protozoan diseases affecting the GI tract

Like other microbes, protozoa are abundant in natural microbiota but can also be associated with significant illness. Gastrointestinal diseases caused by protozoa are generally associated with exposure to contaminated food and water, meaning that those without access to good sanitation are at greatest risk. Even in developed countries, infections can occur and these microbes have sometimes caused significant outbreaks from contamination of public water supplies.

## Giardiasis

Also called backpacker's diarrhea or beaver fever, giardiasis is a common disease in the United States caused by the flagellated protist *Giardia lamblia*, also known as *Giardia intestinalis* or *Giardia duodenalis* (Figure 1.3.5). To establish infection, *G. lamblia* uses a large adhesive disk to attach to the intestinal mucosa. The disk is comprised of microtubules. During adhesion, the flagella of *G. lamblia* move in a manner that draws fluid out from under the disk, resulting in an area of lower pressure that promotes its adhesion to the intestinal epithelial cells. Due to its attachment, *Giardia* also blocks absorption of nutrients, including fats.

Transmission occurs through contaminated food or water or directly from person to person. Children in day-care centers are at risk due to their tendency to put items into their mouths that may be contaminated. Large outbreaks may occur if a public water supply becomes contaminated. *Giardia* have a resistant cyst stage in their life cycle that is able to survive cold temperatures and the chlorination treatment typically used for drinking water in municipal reservoirs. As a result, municipal water must be filtered to trap and remove these cysts. Once consumed by the host, *Giardia* develops into the active tropozoite.

Infected individuals may be asymptomatic or have gastrointestinal signs and symptoms, sometimes accompanied by weight loss. Common symptoms, which appear one to three weeks after exposure, include diarrhea, nausea, stomach cramps, gas, greasy stool (because fat absorption is being blocked), and possible dehydration. The parasite remains in the colon and does not cause systemic infection. Signs and symptoms generally clear within two to six weeks. Chronic infections may develop and are often resistant to treatment. These are associated with weight loss, episodic diarrhea, and malabsorption syndrome due to the blocked nutrient absorption.

Diagnosis may be made using observation under the microscope. A stool ova and parasite (O&P) exam involves direct examination of a stool sample for the presence of cysts and trophozoites; it can be used to distinguish common parasitic intestinal infections. ELISA and other immunoassay tests, including commercial direct fluorescence antibody kits, are also used. The most common treatments use metronidazole as the first-line choice, followed by tinidazole. If the infection becomes chronic, the parasites may become resistant to medications.

## Cryptosporidiosis

Another protozoan intestinal illness is cryptosporidiosis, which is usually caused by *Cryptosporidium parvum* or *C. hominis*. (Figure 11.5.1) These pathogens are commonly found in animals and can be spread in feces from mice, birds, and farm animals. Contaminated water and food are most commonly responsible for transmission. The protozoan can also be transmitted through human contact with infected animals or their feces.

In the United States, outbreaks of cryptosporidiosis generally occur through contamination of the public water supply or contaminated water at water parks, swimming pools, and day-care centers. The risk is greatest in areas with poor sanitation, making the disease more common in developing countries.

Signs and symptoms include watery diarrhea, nausea, vomiting, cramps, fever, dehydration, and weight loss. The illness is generally self-limiting within a month. However, immunocompromised patients, such as those with HIV/AIDS, are at particular risk of severe illness or death.

Diagnosis involves direct examination of stool samples, often over multiple days. As with giardiasis, a stool O&P exam may be helpful. Acid fast staining is often used. Enzyme immunoassays and molecular analysis (PCR) are available.

The first line of treatment is typically oral rehydration therapy. Medications are sometimes used to treat the diarrhea. The broad-range anti-parasitic drug nitazoxanide can be used to treat cryptosporidiosis. Other anti-parasitic drugs that can be used include azithromycin and paromomycin.

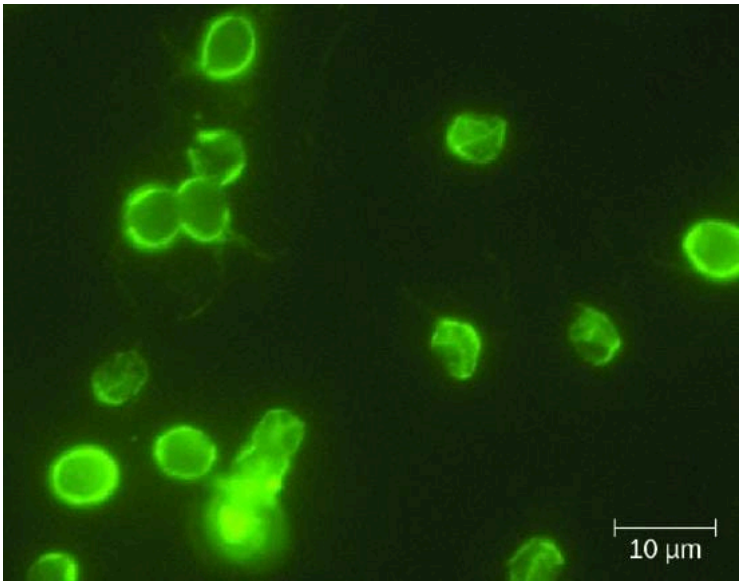



Figure 11.5.1: Immunofluorescent staining allows for visualization of *Cryptosporidium* spp. (credit: modification of work by EPA/H.D.A. Lindquist)

## Amoebiasis (Amebiasis)

The protozoan parasite *Entamoeba histolytica* causes amoebiasis, which is known as amoebic dysentery in severe cases. *E. histolytica* is generally transmitted through water or food that has fecal contamination. The disease is most widespread in the developing world and is one of the leading causes of mortality from parasitic disease worldwide. Disease can be caused by as few as 10 cysts being transmitted.

Signs and symptoms range from nonexistent to mild diarrhea to severe amoebic dysentery. Severe infection causes the abdomen to become distended and may be associated with fever. The parasite may live in the colon without causing signs or symptoms or may invade the mucosa to cause colitis. In some cases, the disease spreads to the spleen, brain, genitourinary tract, or lungs. In particular, it may spread to the liver and cause an abscess. When a liver abscess develops, fever, nausea, liver tenderness, weight loss, and pain in the right abdominal quadrant may occur. Chronic infection may occur and is associated with intermittent diarrhea, mucus, pain, flatulence, and weight loss.

Direct examination of fecal specimens may be used for diagnosis. As with cryptosporidiosis, samples are often examined on multiple days. A stool O&P exam of fecal or biopsy specimens may be helpful. Immunoassay, serology, biopsy, molecular, and antibody detection tests are available. Enzyme immunoassay may not distinguish current from past illness. Magnetic resonance imaging (MRI) can be used to detect any liver abscesses. The first line of treatment is metronidazole or tinidazole, followed by diloxanide furoate, iodoquinol, or paromomycin to eliminate the cysts that remain.

## Cyclosporiasis

The intestinal disease cyclosporiasis is caused by the protozoan *Cyclospora cayetanensis*. It is endemic to tropical and subtropical regions and therefore uncommon in the United States, although there have been outbreaks associated with contaminated produce imported from regions where the protozoan is more common. This protist is transmitted through contaminated food and water and reaches the lining of the small intestine, where it causes infection. Signs and symptoms begin within seven to ten days after ingestion. Based on limited data, it appears to be seasonal in ways that differ regionally and that are poorly understood.

Some individuals do not develop signs or symptoms. Those who do may exhibit explosive and watery diarrhea, fever, nausea, vomiting, cramps, loss of appetite, fatigue, and bloating. These symptoms may last for months without treatment. Trimethoprim-sulfamethoxazole is the recommended treatment. Microscopic examination is used for diagnosis. A stool O&P examination may be helpful. The oocysts have a distinctive blue halo when viewed using ultraviolet fluorescence microscopy (Figure 11.5.2).

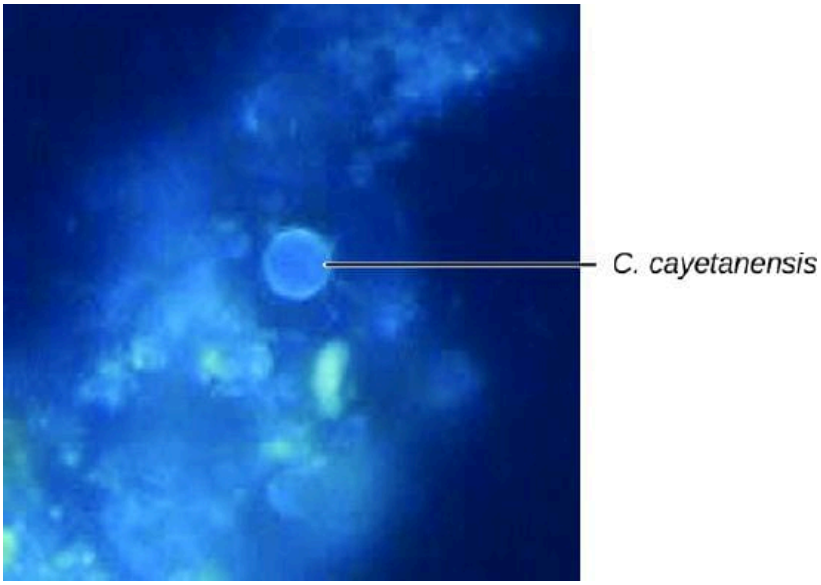



Figure 11.5.2: Cyclospora cayetanensis are autofluorescent under ultraviolet light. (credit: modification of work by Centers for Disease Control and Prevention)

## Exercise 11.5.1

Which protozoan GI infections are common in the United States?

## Protozoan Gastrointestinal Infections

Protozoan GI infections are generally transmitted through contaminated food or water, triggering diarrhea and vomiting that can lead to dehydration. Rehydration therapy is an important aspect of treatment, but most protozoan GI infections can also be treated with drugs that target protozoans.

**Protozoan Infections of the GI Tract**

| Disease | Pathogen | Signs and Symptoms | Transmission | Diagnostic Tests | Antimicrobial Drugs |
|---|---|---|---|---|---|
| Amoebiasis (amoebic dysentery) | *Entamoeba histolytica* | From mild diarrhea to severe dysentery and colitis; may cause abscess on the liver | Fecal-oral route; ingestion of cysts from fecally contaminated water, food, or hands | Stool O&P exam, enzyme immunoassay | Metronidazole, tinidazole, diloxanide furoate, iodoquinol, paromomycin |
| Cryptosporidiosis | *Cryptosporidium parvum, Cryptosporidium hominis* | Watery diarrhea, nausea, vomiting, cramps, fever, dehydration, and weight loss | Contact with feces of infected mice, birds, farm animals; ingestion of contaminated food or water; exposure to contaminated water while swimming or bathing | Stool O&P exam, enzyme immunoassay, PCR | Nitazoxanide, azithromycin, and paromomycin |
| Cyclosporiasis | *Cyclospora cayetanensis* | Explosive diarrhea, fever, nausea, vomiting, cramps, loss of appetite, fatigue, bloating | Ingestion of contaminated food or water | Stool O&P exam using ultraviolet fluorescence microscopy | Trimethoprim-sulfmethoxazole |
| Giardiasis | *Giardia lamblia* | Diarrhea, nausea, stomach cramps, gas, greasy stool, dehydration if severe; sometimes malabsorption syndrome | Contact with infected individual or contaminated fomites; ingestion of contaminated food or water | Stool O&P exam; ELISA, direct fluorescence antibody assays | Metronidazole, tinidazole |

Figure 11.5.3: Protozoan infections of the GI tract.

## Key Concepts and Summary

- **Giardiasis**, **cryptosporidiosis**, **amoebiasis**, and **cyclosporiasis** are intestinal infections caused by protozoans.
- Protozoan intestinal infections are commonly transmitted through contaminated food and water.
- Treatment varies depending on the causative agent, so proper diagnosis is important.
- Microscopic examination of stool or biopsy specimens is often used in diagnosis, in combination with other approaches.

## Footnotes

1. 1 Centers for Disease Control and Prevention. “Cyclosporiasis FAQs for Health Professionals.” Updated June 13, 2014. http://www.cdc.gov/parasites/cyclosp...s/hp-faqs.html.

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# 11: DIGESTIVE SYSTEM INFECTIONS

Gastrointestinal (GI) diseases are so common that, unfortunately, most people have had first-hand experience with the unpleasant symptoms, such as diarrhea, vomiting, and abdominal discomfort. The causes of gastrointestinal illness can vary widely, but such diseases can be grouped into two categories: those caused by infection (the growth of a pathogen in the GI tract) or intoxication (the presence of a microbial toxin in the GI tract).

Foodborne pathogens like *Escherichia coli* O157:H7 are among the most common sources of gastrointestinal disease. Contaminated food and water have always posed a health risk for humans, but in today's global economy, outbreaks can occur on a much larger scale. *E. coli* O157:H7 is a potentially deadly strain of *E. coli* with a history of contaminating meat and produce that are not properly processed. The source of an *E. coli* O157:H7 outbreak can be difficult to trace, especially if the contaminated food is processed in a foreign country. Once the source is identified, authorities may issue recalls of the contaminated food products, but by then there are typically numerous cases of food poisoning, some of them fatal.

## Chapter Outline


11.1: Anatomy and Normal Microbiota of the Digestive System

11.2: Microbial Diseases of the Mouth and Oral Cavity

11.3: Bacterial Infections of the Gastrointestinal Tract

11.4: Viral Infections of the Gastrointestinal Tract

11.5: Protozoan Infections of the Gastrointestinal Tract

11.6: Helminthic Infections of the Gastrointestinal Tract

11.7: Review Questions



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# 11.6: Helminthic Infections of the Gastrointestinal Tract

**Learning Objectives**

- Identify the most common helminths that cause infections of the GI tract
- Compare the major characteristics of specific helminthic diseases affecting GI tract

Helminths are widespread intestinal parasites. These parasites can be divided into three common groups: round-bodied worms also described as nematodes, flat-bodied worms that are segmented (also described as cestodes), and flat-bodied worms that are non-segmented (also described as trematodes). The nematodes include roundworms, pinworms, hookworms, and whipworms. Cestodes include beef, pork, and fish tapeworms. Trematodes are collectively called flukes and more uniquely identified with the body site where the adult flukes are located. Although infection can have serious consequences, many of these parasites are so well adapted to the human host that there is little obvious disease.

## Ascariasis

Infections caused by the large nematode roundworm *Ascaris lumbricoides*, a soil-transmitted helminth, are called ascariasis. Over 800 million to 1 billion people are estimated to be infected worldwide.[1] Infections are most common in warmer climates and at warmer times of year. At present, infections are uncommon in the United States. The eggs of the worms are transmitted through contaminated food and water. This may happen if food is grown in contaminated soil, including when manure is used as fertilizer.

When an individual consumes embryonated eggs (those with a developing embryo), the eggs travel to the intestine and the larvae are able to hatch. *Ascaris* is able to produce proteases that allow for penetration and degradation of host tissue. The juvenile worms can then enter the circulatory system and migrate to the lungs where they enter the alveoli (air sacs). From here they crawl to the pharynx and then follow the gut lumen to return to the small intestine, where they mature into adult roundworms. Females in the host will produce and release eggs that leave the host via feces. In some cases, the worms can block ducts such as those of the pancreas or gallbladder.

The infection is commonly asymptomatic. When signs and symptoms are present, they include shortness of breath, cough, nausea, diarrhea, blood in the stool, abdominal pain, weight loss, and fatigue. The roundworms may be visible in the stool. In severe cases, children with substantial infections may experience intestinal blockage.

The eggs can be identified by microscopic examination of the stool (Figure 11.6.1). In some cases, the worms themselves may be identified if coughed up or excreted in stool. They can also sometimes be identified by X-rays, ultrasounds, or MRIs.

Ascariasis is self-limiting, but can last one to two years because the worms can inhibit the body's inflammatory response through glycan gimmickry (see Virulence Factors of Eukaryotic Pathogens). The first line of treatment is mebendazole or albendazole. In some severe cases, surgery may be required.




(a) (b) (c)

Figure 11.6.1: (a) Adult *Ascaris lumbricoides* roundworms can cause intestinal blockage. (b) This mass of *A. lumbricoides* worms was excreted by a child. (c) A micrograph of a fertilized egg of *A. lumbricoides*. Fertilized eggs can be distinguished from unfertilized eggs because they are round rather than elongated and have a thicker cell wall. (credit a: modification of work by South African Medical Research Council; credit b: modification of work by James Gathany, Centers for Disease Control and Prevention; credit c: modification of work by Centers for Disease Control and Prevention)

**Exercise 11.6.1**

Describe the route by which *A. lumbricoides* reaches the host's intestines as an adult worm.

## Hookworm

Two species of nematode worms are associated with hookworm infection. Both species are found in the Americas, Africa, and Asia. *Necator americanus* is found predominantly in the United States and Australia. Another species, *Ancylostoma doudenale*, is found in southern Europe, North Africa, the Middle East, and Asia. The eggs of these species develop into larvae in soil contaminated by dog or cat feces. These larvae can penetrate the skin. After traveling through the venous circulation, they reach the lungs. When they are coughed up, they are then swallowed and can enter the intestine and develop into mature adults. At this stage, they attach to the wall of the intestine, where they feed on blood and can potentially cause anemia. Signs and symptoms include cough, an itchy rash, loss of appetite, abdominal pain, and diarrhea. In children, hookworms can affect physical and cognitive growth.

Some hookworm species, such as *Ancylostoma braziliense* that is commonly found in animals such as cats and dogs, can penetrate human skin and migrate, causing cutaneous larva migrans, a skin disease caused by the larvae of hookworms. As they move across the skin, in the subcutaneous tissue, pruritic tracks appear (Figure 11.6.2).



(a) (b) (c)

Figure 11.6.2: (a) This animal hookworm, *Ancylostoma caninum*, is attached to the intestinal wall. (b) The tracks of hookworms are visible in this individual with cutaneous larva migrans. (c) This micrograph shows the microscopic egg of a hookworm. (credit a, c: modification of work by Centers for Disease Control and Prevention).

The infection is diagnosed using microscopic examination of the stool, allowing for observation of eggs in the feces. Medications such as albendazole, mebendazole, and pyrantel pamoate are used as needed to treat systemic infection. In addition to systemic

medication for symptoms associated with cutaneous larva migrans, topical thiabendazole is applied to the affected areas.

## Strongyloidiasis

Strongyloidiasis is generally caused by *Strongyloides stercoralis*, a soil-transmitted helminth with both free-living and parasitic forms. In the parasitic form, the larvae of these nematodes generally penetrate the body through the skin, especially through bare feet, although transmission through organ transplantation or at facilities like day-care centers can also occur. When excreted in the stool, larvae can become free-living adults rather than developing into the parasitic form. These free-living worms reproduce, laying eggs that hatch into larvae that can develop into the parasitic form. In the parasitic life cycle, infective larvae enter the skin, generally through the feet. The larvae reach the circulatory system, which allows them to travel to the alveolar spaces of the lungs. They are transported to the pharynx where, like many other helminths, the infected patient coughs them up and swallows them again so that they return to the intestine. Once they reach the intestine, females live in the epithelium and produce eggs that develop asexually, unlike the free-living forms, which use sexual reproduction. The larvae may be excreted in the stool or can reinfect the host by entering the tissue of the intestines and skin around the anus, which can lead to chronic infections.

The condition is generally asymptomatic, although severe symptoms can develop after treatment with corticosteroids for asthma or chronic obstructive pulmonary disease, or following other forms of immunosuppression. When the immune system is suppressed, the rate of autoinfection increases, and huge amounts of larvae migrate to organs throughout the body.

Signs and symptoms are generally nonspecific. The condition can cause a rash at the site of skin entry, cough (dry or with blood), fever, nausea, difficulty breathing, bloating, pain, heartburn, and, rarely, arthritis, or cardiac or kidney complications. Disseminated strongyloidiasis or hyperinfection is a life-threatening form of the disease that can occur, usually following immunosuppression such as that caused by glucocorticoid treatment (most commonly), with other immunosuppressive medications, with HIV infection, or with malnutrition.

As with other helminths, direct examination of the stool is important in diagnosis. Ideally, this should be continued over seven days. Serological testing, including antigen testing, is also available. These can be limited by cross-reactions with other similar parasites and by the inability to distinguish current from resolved infection. Ivermectin is the preferred treatment, with albendazole as a secondary option.

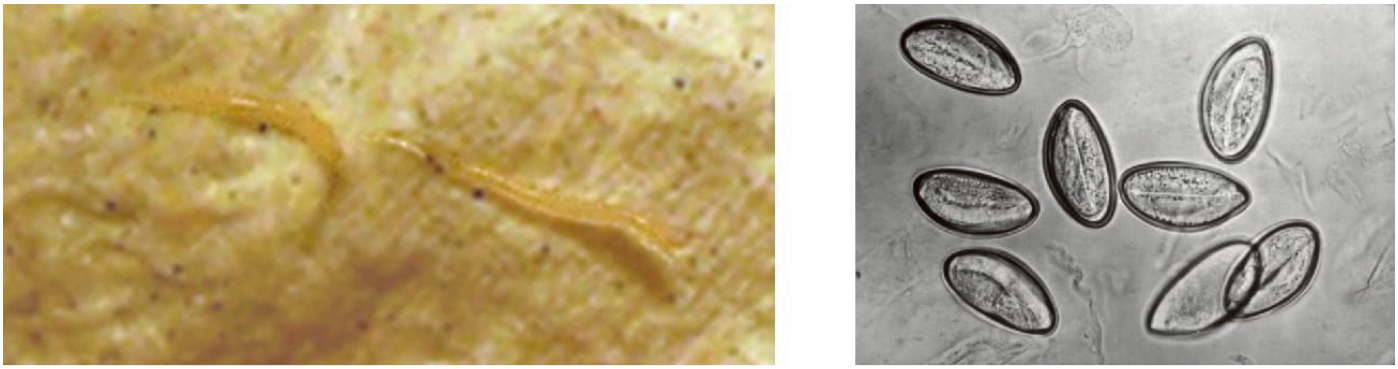
**Exercise 11.6.2**

How does an acute infection of *S. stercoralis* become chronic?

## Pinworms (Enterobiasis)

*Enterobius vermicularis*, commonly called pinworms, are tiny (2–13 mm) nematodes that cause enterobiasis. Of all helminthic infections, enterobiasis is the most common in the United States, affecting as many as one-third of American children.[2] Although the signs and symptoms are generally mild, patients may experience abdominal pain and insomnia from itching of the perianal region, which frequently occurs at night when worms leave the anus to lay eggs. The itching contributes to transmission, as the disease is transmitted through the fecal-oral route. When an infected individual scratches the anal area, eggs may get under the fingernails and later be deposited near the individual's mouth, causing reinfection, or on fomites, where they can be transferred to new hosts. After being ingested, the larvae hatch within the small intestine and then take up residence in the colon and develop into adults. From the colon, the female adult exits the body at night to lay eggs (Figure 11.6.3).

Infection is diagnosed in any of three ways. First, because the worms emerge at night to lay eggs, it is possible to inspect the perianal region for worms while an individual is asleep. An alternative is to use transparent tape to remove eggs from the area around the anus first thing in the morning for three days to yield eggs for microscopic examination. Finally, it may be possible to detect eggs through examination of samples from under the fingernails, where eggs may lodge due to scratching. Once diagnosis has been made, mebendazole, albendazole, and pyrantel pamoate are effective for treatment.



(a) (b)

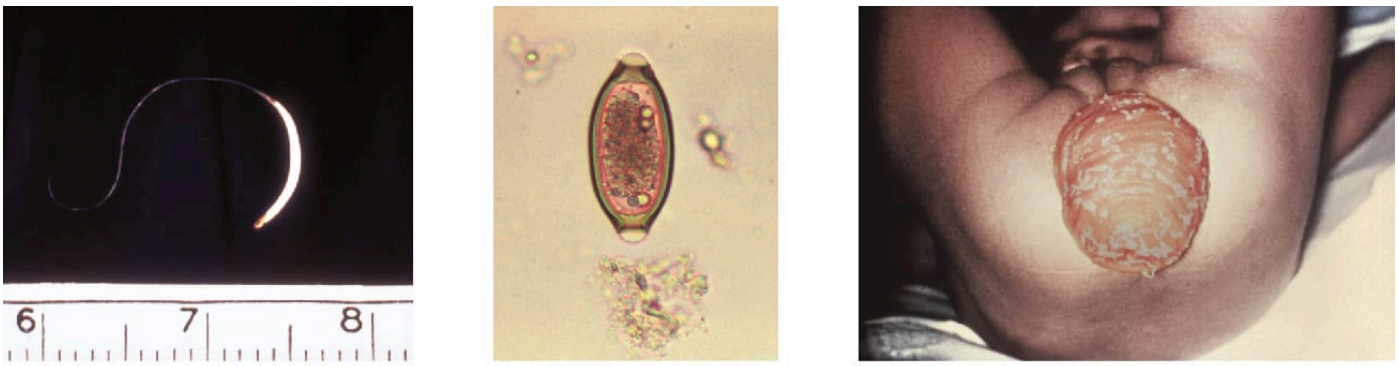
Figure 11.6.3: (a) *E. vermicularis* are tiny nematodes commonly called pinworms. (b) This micrograph shows pinworm eggs.

## Trichuriasis

The nematode whipworm *Trichuris trichiura* is a parasite that is transmitted by ingestion from soil-contaminated hands or food and causes trichuriasis. Infection is most common in warm environments, especially when there is poor sanitation and greater risk of fecal contamination of soil, or when food is grown in soil using manure as a fertilizer. The signs and symptoms may be minimal or nonexistent. When a substantial infection develops, signs and symptoms include painful, frequent diarrhea that may contain mucus and blood. It is possible for the infection to cause rectal prolapse, a condition in which a portion of the rectum becomes detached from the inside of the body and protrudes from the anus (Figure 11.6.4). Severely infected children may experience reduced growth and their cognitive development may be affected.

When fertilized eggs are ingested, they travel to the intestine and the larvae emerge, taking up residence in the walls of the colon and cecum. They attach themselves with part of their bodies embedded in the mucosa. The larvae mature and live in the cecum and ascending colon. After 60 to 70 days, females begin to lay 3000 to 20,000 eggs per day.

Diagnosis involves examination of the feces for the presence of eggs. It may be necessary to use concentration techniques and to collect specimens on multiple days. Following diagnosis, the infection may be treated with mebendazole, albendazole, or ivermectin.




(a) (b) (c)

Figure 11.6.4: (a) This adult female *Trichuris* whipworm is a soil-transmitted parasite. (b) *Trichuris trichiura* eggs are ingested and travel to the intestines where the larvae emerge and take up residence. (c) Rectal prolapse is a condition that can result from whipworm infections. It occurs when the rectum loses its attachment to the internal body structure and protrudes from the anus. (credit a, b, c: modification of work by Centers for Disease Control and Prevention)

## Trichinosis

Trichinosis (trichenellosis) develops following consumption of food that contains *Trichinella spiralis* (most commonly) or other *Trichinella* species. These microscopic nematode worms are most commonly transmitted in meat, especially pork, that has not been cooked thoroughly. *T. spiralis* larvae in meat emerge from cysts when exposed to acid and pepsin in the stomach. They

develop into mature adults within the large intestine. The larvae produced in the large intestine are able to migrate into the muscles mechanically via the stylet of the parasite, forming cysts. Muscle proteins are reduced in abundance or undetectable in cells that contain *Trichinella* (nurse cells). Animals that ingest the cysts from other animals can later develop infection (Figure 11.6.5).

Although infection may be asymptomatic, symptomatic infections begin within a day or two of consuming the nematodes. Abdominal symptoms arise first and can include diarrhea, constipation, and abdominal pain. Other possible symptoms include headache, light sensitivity, muscle pain, fever, cough, chills, and conjunctivitis. More severe symptoms affecting motor coordination, breathing, and the heart sometimes occur. It may take months for the symptoms to resolve, and the condition is occasionally fatal. Mild cases may be mistaken for influenza or similar conditions.

Infection is diagnosed using clinical history, muscle biopsy to look for larvae, and serological testing, including immunoassays. Enzyme immunoassay is the most common test. It is difficult to effectively treat larvae that have formed cysts in the muscle, although medications may help. It is best to begin treatment as soon as possible because medications such as mebendazole and albendazole are effective in killing only the adult worms in the intestine. Steroids may be used to reduce inflammation if larvae are in the muscles.

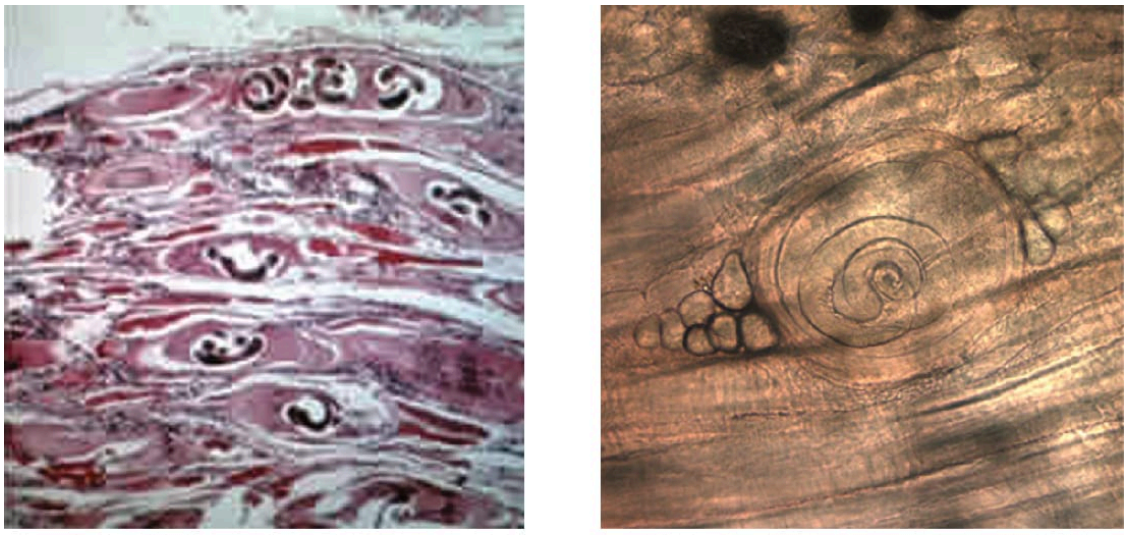



Figure 11.6.5: (a) This image shows larvae of *T. spiralis* within muscle. (b) In meat, the larvae have a characteristic coiled appearance, as seen in this partially digested larva in bear meat. (credit a, b: modification of work by Centers for Disease Control and Prevention)

**Exercise 11.6.3**

Compare and contrast the transmissions of pinworms and whipworms.

## Tapeworms (Taeniasis)

Taeniasis is a tapeworm infection, generally caused by pork (*Taenia solium*), beef (*Taenia saginata*), and Asian (*Taenia asiatica*) tapeworms found in undercooked meat. Consumption of raw or undercooked fish, including contaminated sushi, can also result in infection from the fish tapeworm (*Diphyllobothrium latum*). Tapeworms are flatworms (cestodes) with multiple body segments and a head called a scolex that attaches to the intestinal wall. Tapeworms can become quite large, reaching 4 to 8 meters long (Figure 11.6.6). Figure 5.2.5 illustrates the life cycle of a tapeworm.

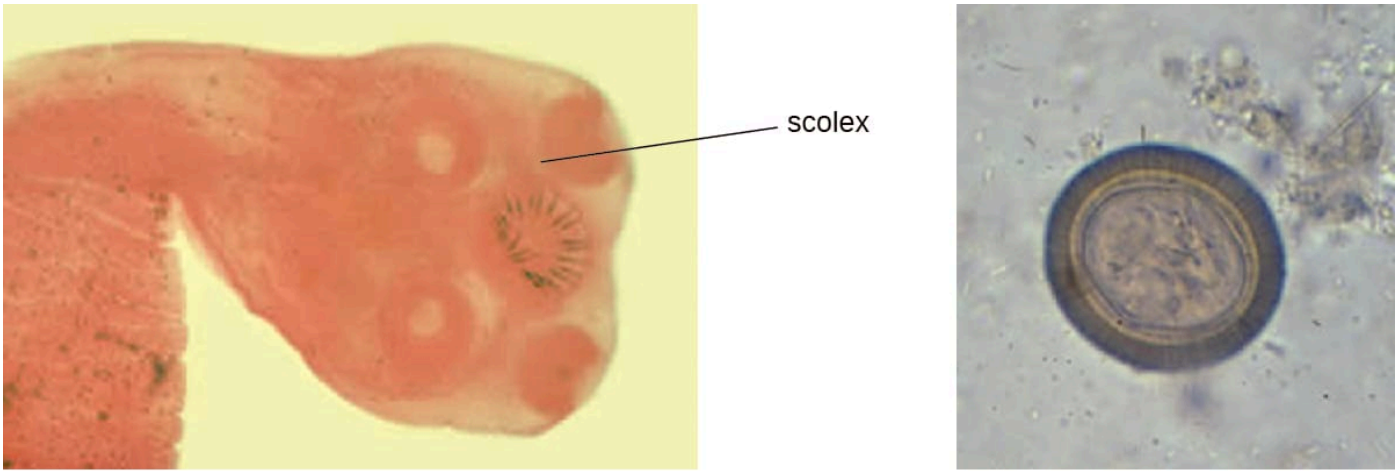



Figure 11.6.6: (a) An adult tapeworm uses the scolex to attach to the intestinal wall. (b) The egg of a pork tapeworm (*Taenia solium*) is visible in this micrograph. (credit a, b: modification of work by Centers for Disease Control and Prevention)

Tapeworms attached to the intestinal wall produce eggs that are excreted in feces. After ingestion by animals, the eggs hatch and the larvae emerge. They may take up residence in the intestine, but can sometimes move to other tissues, especially muscle or brain tissue. When *T. solium* larvae form cysts in tissue, the condition is called cysticercosis. This occurs through ingestion of eggs via the fecal-oral route, not through consumption of undercooked meat. It can develop in the muscles, eye (ophthalmic cysticercosis), or brain (neurocysticercosis).

Infections may be asymptomatic or they may cause mild gastrointestinal symptoms such as epigastric discomfort, nausea, diarrhea, flatulence, or hunger pains. It is also common to find visible tapeworm segments passed in the stool. In cases of cysticercosis, symptoms differ depending upon where the cysts become established. Neurocysticercosis can have severe, life-threatening consequences and is associated with headaches and seizures because of the presence of the tapeworm larvae encysted in the brain. Cysts in muscles may be asymptomatic, or they may be painful.

To diagnose these conditions, microscopic analysis of stool samples from three separate days is generally recommended. Eggs or body segments, called proglottids, may be visible in these samples. Molecular methods have been developed but are not yet widely available. Imaging, such as CT and MRI, may be used to detect cysts. Praziquantel or niclosamide are used for treatment.

### What's in Your Sushi Roll?

As foods that contain raw fish, such as sushi and sashimi, continue to increase in popularity throughout the world, so does the risk of parasitic infections carried by raw or undercooked fish. *Diphyllobothrium* species, known as fish tapeworms, is one of the main culprits. Evidence suggests that undercooked salmon caused an increase in *Diphyllobothrium* infections in British Columbia in the 1970s and early 1980s. In the years since, the number of reported cases in the United States and Canada has been low, but it is likely that cases are underreported because the causative agent is not easily recognized.[3]

Another illness transmitted in undercooked fish is herring worm disease, or anisakiasis, in which nematodes attach to the epithelium of the esophagus, stomach, or small intestine. Cases have increased around the world as raw fish consumption has increased.[4]

Although the message may be unpopular with sushi lovers, fish should be frozen or cooked before eating. The extremely low and high temperatures associated with freezing and cooking kill worms and larvae contained in the meat, thereby preventing infection. Ingesting fresh, raw sushi may make for a delightful meal, but it also entails some risk.

## Hydatid Disease

Another cestode, *Echinococcus granulosus*, causes a serious infection known as hydatid disease (cystic echinococcosis). *E. granulosus* is found in dogs (the definitive host), as well as several intermediate hosts (sheep, pigs, goats, cattle). The cestodes

are transmitted through eggs in the feces from infected animals, which can be an occupational hazard for individuals who work in agriculture.

Once ingested, *E. granulosus* eggs hatch in the small intestine and release the larvae. The larvae invade the intestinal wall to gain access to the circulatory system. They form hydatid cysts in internal organs, especially in the lungs and liver, that grow slowly and are often undetected until they become large. If the cysts burst, a severe allergic reaction (anaphylaxis) may occur.

Cysts present in the liver can cause enlargement of the liver, nausea, vomiting, right epigastric pain, pain in the right upper quadrant, and possible allergic signs and symptoms. Cysts in the lungs can lead to alveolar disease. Abdominal pain, weight loss, pain, and malaise may occur, and inflammatory processes develop.

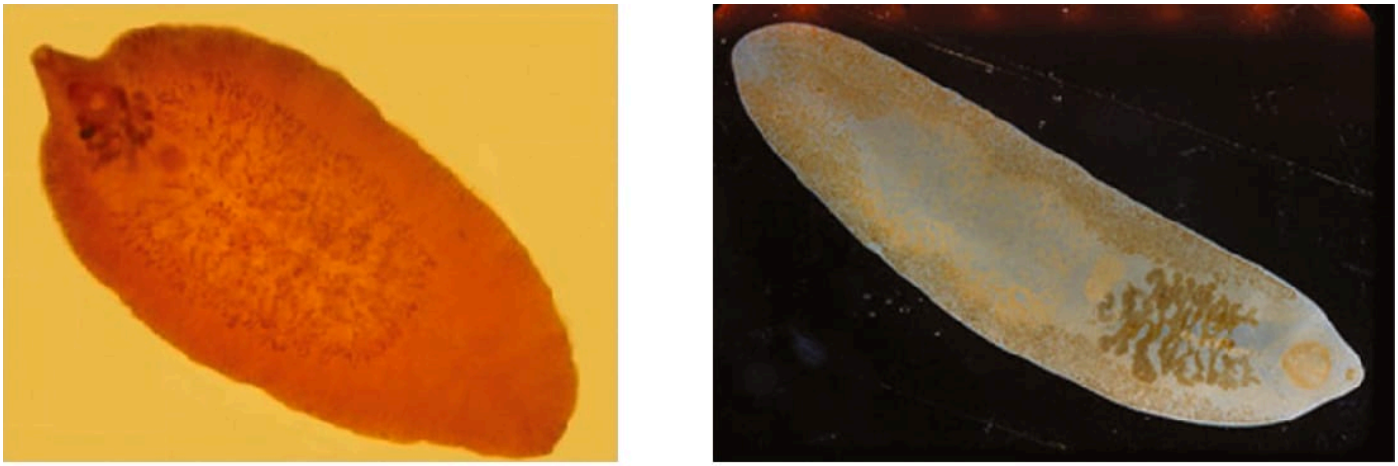
*E. granulosus* can be detected through imaging (ultrasonography, CT, MRI) that shows the cysts. Serologic tests, including ELISA and indirect hemagglutinin tests, are used. Cystic disease is most effectively treated with surgery to remove cysts, but other treatments are also available, including chemotherapy with anti-helminthic drugs (albendazoleor mebendazole).

**Exercise 11.6.4**

Describe the risks of the cysts associated with taeniasis and hydatid disease.

## Flukes

Flukes are flatworms that have a leaflike appearance. They are a type of trematode worm, and multiple species are associated with disease in humans. The most common are liver flukes and intestinal flukes (Figure 11.6.7).



(a) (b)

Figure 11.6.7: (a) A liver fluke infects the bile ducts. (b) An intestinal fluke infects the intestines. (credit a: modification of work by Shafiei R, Sarkari B, Sadjjadi SM, Mowlavi GR, and Moshfe A; credit b: modification of work by Georgia Division of Public Health)

## Liver Flukes

The liver flukes are several species of trematodes that cause disease by interfering with the bile duct. Fascioliasis is caused by *Fasciola hepatica* and *Fasciola gigantica* in contaminated raw or undercooked aquatic plants (e.g., watercress). In *Fasciola* infection, adult flukes develop in the bile duct and release eggs into the feces. Clonochiasis is caused by *Clonorchis sinensis* in contaminated freshwater fish. Other flukes, such as *Opisthorchis viverrini* (found in fish) and *Opisthorchis felineus* (found in freshwater snails), also cause infections. Liver flukes spend part of their life cycle in freshwater snails, which serve as an intermediate host. Humans are typically infected after eating aquatic plants contaminated by the infective larvae after they have left the snail. Once they reach the human intestine, they migrate back to the bile duct, where they mature. The life cycle is similar for the other infectious liver flukes (see Figure 5.2.4).

When *Fasciola* flukes cause acute infection, signs and symptoms include nausea, vomiting, abdominal pain, rash, fever, malaise,

and breathing difficulties. If the infection becomes chronic, with adult flukes living in the bile duct, then cholangitis, cirrhosis, pancreatitis, cholecystitis, and gallstones may develop. Symptoms are similar for infections by other liver flukes. Cholangiocarcinoma can occur from *C. sinensis* infection. The *Opisthorchis* species can also be associated with cancer development.

Diagnosis is accomplished using patient history and examination of samples from feces or other samples (such as vomitus). Because the eggs may appear similar, immunoassay techniques are available that can help distinguish species. The preferred treatment for fascioliasis is triclabendazole. *C. sinensis* and *Opisthorchis* spp. infections are treated with praziquantel or albendazole.

## Intestinal Flukes

The intestinal flukes are trematodes that develop in the intestines. Many, such as *Fasciolopsis buski*, which causes fasciolopsiasis, are closely related to liver flukes. Intestinal flukes are ingested from contaminated aquatic plants that have not been properly cooked. When the cysts are consumed, the larvae emerge in the duodenum and develop into adults while attached to the intestinal epithelium. The eggs are released in stool.

Intestinal fluke infection is often asymptomatic, but some cases may involve mild diarrhea and abdominal pain. More severe symptoms such as vomiting, nausea, allergic reactions, and anemia can sometimes occur, and high parasite loads may sometimes lead to intestinal obstructions.

Diagnosis is the same as with liver flukes: examination of feces or other samples and immunoassay. Praziquantel is used to treat infections caused by intestinal flukes.

### Exercise 11.6.5

How are flukes transmitted?

### Helminthic Gastrointestinal Infections

Numerous helminths are capable of colonizing the GI tract. Many such infections are asymptomatic, but others may cause signs and symptoms ranging from mild GI stress to severe systemic infection. Helminths have complex and unique life cycles that dictate their specific modes of transmission. Most helminthic infections can be treated with medications.

**Common Helminthic Infections of the GI Tract**

| Disease | Causative Agent(s) | Mode of Transmission | Laboratory Tests | Symptoms | Treatments |
|---|---|---|---|---|---|
| Ascariasis | *Ascaris lumbricoides* | Eggs in fecally contaminated food or water | Microscopic examination of the stool, imaging | Shortness of breath, cough, nausea, diarrhea, blood in stool, abdominal pain, weight loss, fatigue | Self-limiting within 1 to 2 years; albendazole and mebendazole if needed |
| Hookworm | *Necator americanus*, *Ancylostoma duodenale* | Larvae in soil contaminated by dog or cat feces penetrate skin | Microscopic examination of stool (may require a concentration procedure) | Cough, itchy rash, loss of appetite, abdominal pain, diarrhea; in children, may affect physical and cognitive growth | Albendazole and mebendazole; pyrantel pamoatemay if needed |
| Strongyloidiasis | *Strongyloides stercoralis* | Soil-dwelling larvae penetrate the skin, usually bare feet | Microscopic examination of stool over several days (ideally at least 7); some serologic testing available | Often asymptomatic; cough (sometimes bloody), skin rash, abdominal pain, and diarrhea; in immunosuppressed patients, may become disseminated, causing serious and potentially fatal complications | Ivermectin (preferred), albendazole |
| Enterobiasis (pinworm) | *Enterobius vermicularis* | Fecal–oral route | Observation of eggs or worms from anal area; examination of samples under fingernails | Itching around the anus, abdominal pain, insomnia, irritation of female genital tract | Mebendazole, albendazole, pyrantel pamoate |
| Trichiuriasis (whipworm) | *Trichuris trichiura* | Fecal contamination or fertilization in soil | Microscopic examination of stool | Abdominal pain, anemia, diarrhea that may be bloody | Albendazole, mebendazole, ivermectin if needed |
| Trichinosis | *Trichinella spiralis* | Eating raw or undercooked pork or other meat of infected animal | Clinical history, muscle biopsy, serological testing, enzyme immunoassay | Diarrhea, constipation, abdominal pain, headache, cough, chills, light sensitivity, muscle pain, fever, conjunctivitis; in severe cases may affect motor coordination, breathing, heart function | Albendazole, mebendazole if needed |
| Taeniasis and cysticercosis | *Taenia solium*, *T. saginata*, *T. asiatica*, *Diphyllobothrium latum* | Eating raw or undercooked beef or pork from infected animal | Observation of worm segments or microscopic eggs in stool samples | Asymptomatic or mild GI distress; cysts in muscle, eye, or brain (cysticercosis); brain cysts can cause headaches, seizures, or death | Praziquantel or niclosamide |
| Cystic echinococcosis (hydatid disease) | *Echinococcus granulosus* (cystic) | Exposure to eggs in feces of infected dogs or livestock | Imaging; serological testing including ELISA and indirect hemagglutinin test | Cysts in lungs, liver, and other organs causing nausea, GI distress, and weight loss; severe anaphylaxis or death if cysts burst | Surgical removal or aspiration of cysts or chemotherapy with albendazole or mebenazole |
| Liver fluke infections | *Fasciola hepatica*, *F. gigantica*, *Clonorchis sinensis*, *Opisthorchis viverrini*, *O. felineus* | Eating raw or undercooked aquatic plants (*Fasciola* spp.) or freshwater fish (*Clonorchis* spp.) contaminated with eggs or cysts | Microscopic examination of eggs in stool or other samples; immunoassays | Fever, malaise, anemia, abdominal symptoms, transaminitis; cholangitis, cirrhosis, pancreatitis, cholecystitis, gall stones in chronic phase | Triclabendazole (preferred) for *Fasciola* spp.; praziquantel and albendazole for *C. sinensis* and *Opisthorchis* spp. |
| Fasciolopiasis (intestinal fluke) | *Fasciola buski* | Eating raw or undercooked aquatic plants containing cysts | Microscopic examination of eggs in stool or other samples; immunoassays | Diarrhea, abdominal pain; in severe cases, vomiting, nausea, intestinal obstruction, anemia, allergic reactions | Praziquantel |

Figure 11.6.8: Helminthic infections of the GI tract.

| Helminthic Infections of the GI Tract (continued) | | | | | |
|---|---|---|---|---|---|
| **Disease** | **Pathogen** | **Signs and Symptoms** | **Transmission** | **Diagnostic Tests** | **Antimicrobial Drugs** |
| Strongyloidiasis | *Strongyloides stercoralis* | Often asymptomatic; cough (sometimes bloody), skin rash, abdominal pain, diarrhea; in immunosuppressed patients, may become disseminated, causing serious and potentially fatal complications | Soil-dwelling larvae penetrate the skin, usually bare feet | Microscopic observation of larvae in stool; serological testing for antigens | Ivermectin, albendazole |
| Tapeworms (taeniasis) | *Taenia solium, T. saginata, T. asiatica, Diphyllobothrium latum* | Asymptomatic or mild GI distress; cysts in muscle, eye, or brain (cysticercosis); brain cysts can cause headaches, seizures, or death | Ingestion of raw or undercooked pork or beef from infected animal | Observation of worm segments or microscopic eggs in stool; CT or MRI to detect cysts | Praziquantel, niclosamide |
| Trichinosis | *Trichinella spiralis*, other *Trichinella* spp. | Diarrhea, constipation, abdominal pain, headache, cough, chills, light sensitivity, muscle pain, fever, conjunctivitis; in severe cases may affect motor coordination, breathing, heart function | Ingestion of raw or undercooked pork or other meat of infected animal | Observation of cysts in muscle biopsy, enzyme immunoassay | Albendazole, mebendazole |
| Whipworm (trichuriasis) | *Trichuris trichiura* | Abdominal pain, anemia, diarrhea (possibly bloody), rectal prolapse | Ingestion of eggs in fecally contaminated food | Microscopic observation of eggs in stool | Albendazole, mebendazole, ivermectin |

Figure 11.6.9: Helminthic infections of the GI tract (continued).

## Clinical Focus: Resolution

Carli's doctor explained that she had bacterial gastroenteritis caused by *Salmonella* bacteria. The source of these bacteria was likely the undercooked egg. Had the egg been fully cooked, the high temperature would have been sufficient to kill any *Salmonella* in or on the egg. In this case, enough bacteria survived to cause an infection once the egg was eaten.

Carli's signs and symptoms continued to worsen. Her fever became higher, her vomiting and diarrhea continued, and she began to become dehydrated. She felt thirsty all the time and had continual abdominal cramps. Carli's doctor treated her with intravenous fluids to help with her dehydration, but did not prescribe antibiotics. Carli's parents were confused because they thought a bacterial infection should always be treated with antibiotics.

The doctor explained that the worst medical problem for Carli was dehydration. Except in the most vulnerable and sick patients, such as those with HIV/AIDS, antibiotics do not reduce recovery time or improve outcomes in *Salmonella* infections. In fact, antibiotics can actually delay the natural excretion of bacteria from the body. Rehydration therapy replenishes lost fluids, diminishing the effects of dehydration and improving the patient's condition while the infection resolves.

After two days of rehydration therapy, Carli's signs and symptoms began to fade. She was still somewhat thirsty, but the amount of urine she passed became larger and the color lighter. She stopped vomiting. Her fever was gone, and so was the diarrhea. At that point, stool analysis found very few *Salmonella* bacteria. In one week, Carli was discharged as fully recovered.

# Key Concepts and Summary

- Helminths often cause intestinal infections after transmission to humans through exposure to contaminated soil, water, or food. Signs and symptoms are often mild, but severe complications may develop in some cases.
- *Ascaris lumbricoides* eggs are transmitted through contaminated food or water and hatch in the intestine. Juvenile larvae travel to the lungs and then to the pharynx, where they are swallowed and returned to the intestines to mature. These nematode roundworms cause **ascariasis**.
- *Necator americanus* and *Ancylostoma doudenale* cause **hookworm infection** when larvae penetrate the skin from soil contaminated by dog or cat feces. They travel to the lungs and are then swallowed to mature in the intestines.
- *Strongyloides stercoralis* are transmitted from soil through the skin to the lungs and then to the intestine where they cause **strongyloidiasis**.
- *Enterobius vermicularis* are nematode pinworms transmitted by the fecal-oral route. After ingestion, they travel to the colon where they cause **enterobiasis**.
- *Trichuris trichiura* can be transmitted through soil or fecal contamination and cause **trichuriasis**. After ingestion, the eggs travel to the intestine where the larvae emerge and mature, attaching to the walls of the colon and cecum.

- *Trichinella* spp. is transmitted through undercooked meat. Larvae in the meat emerge from cysts and mature in the large intestine. They can migrate to the muscles and form new cysts, causing **trichinosis**.
- *Taenia* spp. and *Diphyllobothrium latum* are tapeworms transmitted through undercooked food or the fecal-oral route. *Taenia* infections cause **taeniasis**. Tapeworms use their scolex to attach to the intestinal wall. Larvae may also move to muscle or brain tissue.
- *Echinococcus granulosus* is a cestode transmitted through eggs in the feces of infected animals, especially dogs. After ingestion, eggs hatch in the small intestine, and the larvae invade the intestinal wall and travel through the circulatory system to form dangerous cysts in internal organs, causing **hydatid disease**.
- Flukes are transmitted through aquatic plants or fish. **Liver flukes** cause disease by interfering with the bile duct. **Intestinal flukes** develop in the intestines, where they attach to the intestinal epithelium.

## Footnotes

1. 1 Centers for Disease Control and Prevention. “Parasites–Ascariasis.” Updated May 24, 2016. http://www.cdc.gov/parasites/ascariasis/index.html.
2. 2 “Roundworms.” *University of Maryland Medical Center Medical Reference Guide*. Last reviewed December 9, 2014. https://umm.edu/health/medical/altme...ion/roundworms.
3. 3 Nancy Craig. “Fish Tapeworm and Sushi.” *Canadian Family Physician* 58 (2012) 6: pp. 654–658. www.ncbi.nlm.nih.gov/pmc/articles/PMC3374688/.
4. 4 Centers for Disease Control and Prevention. “Anisakiasis FAQs.” Updated November 12, 2012. http://www.cdc.gov/parasites/anisakiasis/faqs.html.

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# 11.7: Review Questions

## Multiple Choice

1. Which of the following is NOT a way the normal microbiota of the intestine helps to prevent infection?
   A. It produces acids that lower the pH of the stomach.
   B. It speeds up the process by which microbes are flushed from the digestive tract.
   C. It consumes food and occupies space, outcompeting potential pathogens.
   D. It generates large quantities of oxygen that kill anaerobic pathogens.

*Answer available at the end of this section.*

2. What types of microbes live in the intestines?
   A. Diverse species of bacteria, archaea, and fungi, especially *Bacteroides* and *Firmicutes* bacteria
   B. A narrow range of bacteria, especially *Firmicutes*
   C. A narrow range of bacteria and fungi, especially *Bacteroides*
   D. Archaea and fungi only

*Answer available at the end of this section.*

3. What pathogen is the most important contributor to biofilms in plaque?
   A. *Staphylococcus aureus*
   B. *Streptococcus mutans*
   C. *Escherichia coli*
   D. *Clostridium difficile*

*Answer available at the end of this section.*

4. What type of organism causes thrush?
   A. a bacterium
   B. a virus
   C. a fungus
   D. a protozoan

*Answer available at the end of this section.*

5. In mumps, what glands swell to produce the disease's characteristic appearance?
   A. the sublingual glands
   B. the gastric glands
   C. the parotid glands
   D. the submandibular glands

*Answer available at the end of this section.*

6. Which of the following is true of HSV-1?
   A. It causes oral thrush in immunocompromised patients.
   B. Infection is generally self-limiting.
   C. It is a bacterium.
   D. It is usually treated with amoxicillin.

*Answer available at the end of this section.*

7. Which type of *E. coli* infection can be severe with life-threatening consequences such as hemolytic uremic syndrome?
   A. ETEC
   B. EPEC

C. EHEC
D. EIEC

*Answer available at the end of this section.*

8. Which species of *Shigella* has a type that produces Shiga toxin?
   A. *S. boydii*
   B. *S. flexneri*
   C. *S. dysenteriae*
   D. *S. sonnei*

*Answer available at the end of this section.*

9. Which type of bacterium produces an A-B toxin?
   A. *Salmonella*
   B. *Vibrio cholera*
   C. ETEC
   D. *Shigella dysenteriae*

*Answer available at the end of this section.*

10. Which form of hepatitisvirus can only infect an individual who is already infected with another hepatitisvirus?
    A. HDV
    B. HAV
    C. HBV
    D. HEV

*Answer available at the end of this section.*

11. Which cause of viral gastroenteritis commonly causes projectile vomiting?
    A. hepatitisvirus
    B. Astroviruses
    C. Rotavirus
    D. Noroviruses

*Answer available at the end of this section.*

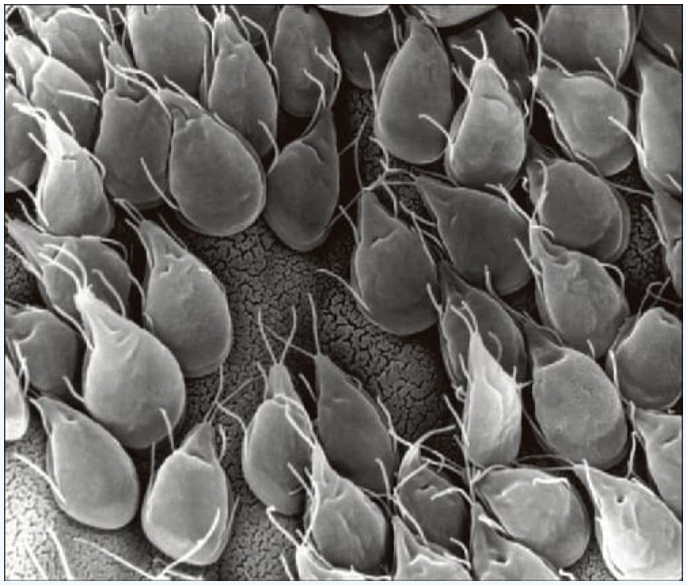
12. Which protozoan is associated with the ability to cause severe dysentery?
    A. *Giardia lamblia*
    B. *Cryptosporidium hominis*
    C. *Cyclospora cayetanesis*
    D. *Entamoeba histolytica*

*Answer available at the end of this section.*

13. Which protozoan has a unique appearance, with a blue halo, when viewed using ultraviolet fluorescence microscopy?
    A. *Giardia lamblia*
    B. *Cryptosporidium hominis*
    C. *Cyclospora cayetanesis*
    D. *Entamoeba histolytica*

*Answer available at the end of this section.*

14. The micrograph shows protozoans attached to the intestinal wall of a gerbil. Based on what you know about protozoan intestinal parasites, what is it?



(credit: Dr. Stan Erlandsen, Centers for Disease Control and Prevention)

A. *Giardia lamblia*
B. *Cryptosporidium hominis*
C. *Cyclospora cayetanesis*
D. *Entamoeba histolytica*

15. What is another name for *Trichuris trichiura*?
A. pinworm
B. whipworm
C. hookworm
D. ascariasis

*Answer available at the end of this section.*

16. Which type of helminth infection can be diagnosed using tape?
A. pinworm
B. whipworm
C. hookworm
D. tapeworm

*Answer available at the end of this section.*

## Fill in the Blank

17. The part of the gastrointestinal tract with the largest natural microbiota is the _____.

*Answer available at the end of this section.*

18. When plaque becomes heavy and hardened, it is called dental calculus or _____.

*Answer available at the end of this section.*

19. Antibiotic associated pseudomembranous colitis is caused by _____.

*Answer available at the end of this section.*

20. Jaundice results from a buildup of _____.

*Answer available at the end of this section.*

21. Chronic _____ infections cause the unique sign of disease of greasy stool and are often resistant to treatment.

*Answer available at the end of this section.*

22. Liver flukes are often found in the _____ duct.

*Answer available at the end of this section.*

## Short Answer

23. How does the diarrhea caused by dysentery differ from other types of diarrhea?
24. Why do sugary foods promote dental caries?
25. Which forms of viral hepatitis are transmitted through the fecal-oral route?
26. What is an O&P exam?
27. Why does the coughing up of worms play an important part in the life cycle of some helminths, such as the roundworm *Ascaris lumbricoides*?

## Critical Thinking

28. Why does use of antibiotics and/or proton pump inhibitors contribute to the development of *C. difficile* infections?
29. Why did scientists initially think it was unlikely that a bacterium caused peptic ulcers?
30. Does it makes a difference in treatment to know if a particular illness is caused by a bacterium (an infection) or a toxin (an intoxication)?
31. Based on what you know about HBV, what are some ways that its transmission could be reduced in a health-care setting?
32. Cases of strongyloidiasis are often more severe in patients who are using corticosteroids to treat another disorder. Explain why this might occur.

## Answers

**Multiple Choice**
D

**Multiple Choice**
A

**Multiple Choice**
B

**Multiple Choice**
C

**Multiple Choice**
C

**Multiple Choice**
B

**Multiple Choice**
C

**Multiple Choice**
C

**Multiple Choice**
B

**Multiple Choice**
A

**Multiple Choice**
D

**Multiple Choice**
D

**Multiple Choice**
C

**Multiple Choice**
B

**Multiple Choice**
A

**Fill in the Blank**
Large intestine or colon

**Fill in the Blank**
tartar

**Fill in the Blank**
*Clostridium difficile*

**Fill in the Blank**
bilirubin

**Fill in the Blank**
giardia

**Fill in the Blank**
bile

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# WEEK 7


## 12: Respiratory System Infections (Part A)

12.1: Viral Infections of the Respiratory Tract

12.2: Review Questions


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# 12.1: Viral Infections of the Respiratory Tract

## Learning Objectives

- Identify the most common viruses that can cause infections of the upper and lower respiratory tract
- Compare the major characteristics of specific viral diseases of the respiratory tract

Viruses are the most frequent cause of respiratory tract infections. Unlike the bacterial pathogens, we have few effective therapies to combat viral respiratory infections. Fortunately, many of these diseases are mild and self-limiting. A few respiratory infections manifest their primary symptoms at other locations in the body.

## The Common Cold

The common cold is a generic term for a variety of mild viral infections of the nasal cavity. More than 200 different viruses are known to cause the common cold. The most common groups of cold viruses include rhinoviruses, coronaviruses, and adenoviruses. These infections are widely disseminated in the human population and are transmitted through direct contact and droplet transmission. Coughing and sneezing efficiently produce infectious aerosols, and rhinoviruses are known to persist on environmental surfaces for up to a week.[1]

Viral contact with the nasal mucosa or eyes can lead to infection. Rhinoviruses tend to replicate best between 33 °C (91.4 °F) and 35 °C (95 °F), somewhat below normal body temperature (37 °C [98.6 °F]). As a consequence, they tend to infect the cooler tissues of the nasal cavities. Colds are marked by an irritation of the mucosa that leads to an inflammatory response. This produces common signs and symptoms such as nasal excess nasal secretions (runny nose), congestion, sore throat, coughing, and sneezing. The absence of high fever is typically used to differentiate common colds from other viral infections, like influenza. Some colds may progress to cause otitis media, pharyngitis, or laryngitis, and patients may also experience headaches and body aches. The disease, however, is self-limiting and typically resolves within 1–2 weeks.

There are no effective antiviral treatments for the common cold and antibacterial drugs should not be prescribed unless secondary bacterial infections have been established. Many of the viruses that cause colds are related, so immunity develops throughout life. Given the number of viruses that cause colds, however, individuals are never likely to develop immunity to all causes of the common cold.

## Exercise 12.1.1

1. How are colds transmitted?
2. What is responsible for the symptoms of a cold?

## Clinical Focus

**Part 3**

Since antibiotic treatment had proven ineffective, John's doctor suspects that a viral or fungal pathogen may be the culprit behind John's case of pneumonia. Another possibility is that John could have an antibiotic-resistant bacterial infection that will require a different antibiotic or combination of antibiotics to clear.

The RIDT tests both came back negative for type A and type B influenza. However, the diagnostic laboratory identified the sputum isolate as *Legionella pneumophila*. The doctor ordered tests of John's urine and, on the second day after his admission, results of an enzyme immunoassay (EIA) were positive for the *Legionella* antigen. John's doctor added levofloxacin to his antibiotic therapy and continued to monitor him. The doctor also began to ask John where he had been over the past 10 to 14 days.

- Do negative RIDT results absolutely rule out influenza virus as the etiologic agent? Why or why not?
- What is John's prognosis?

Jump to the next Clinical Focus box. Go back to the previous Clinical Focus box.

## Influenza

Commonly known as the flu, influenza is a common viral disease of the lower respiratory system caused by an orthomyxovirus. Influenza is pervasive worldwide and causes 3,000–50,000 deaths each year in the United States. The annual mortality rate can vary greatly depending on the virulence of the strain(s) responsible for seasonal epidemics. [2]

Influenza infections are most typically characterized by fever, chills, and body aches. This is followed by symptoms similar to the common cold that may last a week or more. Table 12.1.1 compares the signs and symptoms of influenza and the common cold.

*Table 12.1.1: Comparing the Common Cold and Influenza*

| Sign/Symptom | Common Cold | Influenza |
|---|---|---|
| Fever | Low (37.2 °C [99 °F]) | High (39 °C [102.2 °F]) |
| Headache | Common | Common |
| Aches and pains | Mild | Severe |
| Fatigue | Slight | Severe |
| Nasal congestion | Common | Rare |
| Sneezing | Common | Rare |

In general, influenza is self-limiting. However, serious cases can lead to pneumonia and other complications that can be fatal. Such cases are more common in the very young and the elderly; however, certain strains of influenza virus (like the 1918–1919 variant discussed later in this chapter) are more lethal to young adults than to the very young or old. Strains that affect young adults are believed to involve a cytokine storm—a positive feedback loop that forms between cytokine production and leukocytes. This cytokine storm produces an acute inflammatory response that leads to rapid fluid accumulation in the lungs, culminating in pulmonary failure. In such cases, the ability to mount a vigorous immune response is actually detrimental to the patient. The very young and very old are less susceptible to this effect because their immune systems are less robust.

A complication of influenza that occurs primarily in children and teenagers is Reye syndrome. This sequela causes swelling in the liver and brain, and may progress to neurological damage, coma, or death. Reye syndrome may follow other viral infections, like chickenpox, and has been associated with the use of aspirin. For this reason, the CDC and other agencies recommend that aspirin and products containing aspirin never be used to treat viral illnesses in children younger than age 19 years.[3]

The influenza virus is primarily transmitted by direct contact and inhalation of aerosols. The RNA genome of this virus exists as seven or eight segments, each coated with ribonucleoprotein and encoding one or two specific viral proteins. The influenza virus is surrounded by a lipid membrane envelope, and two of the main antigens of the influenza virus are the spike proteins hemagglutinin (H) and neuraminidase (N), as shown in Figure 12.1.1. These spike proteins play important roles in the viral infectious cycle.

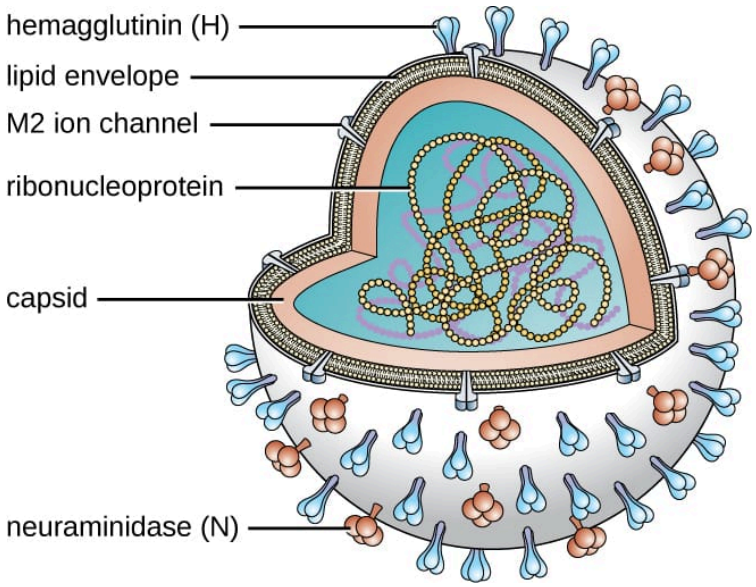



Figure 12.1.1: The illustration shows the structure of an influenza virus. The viral envelope is studded with copies of the proteins neuraminidase and hemagglutinin, and surrounds the individual seven or eight RNA genome segments. (credit: modification of work by Dan Higgins, Centers for Disease Control and Prevention)

Following inhalation, the influenza virus uses the hemagglutinin protein to bind to sialic acid receptors on host respiratory epithelial cells. This facilitates endocytosis of the viral particle. Once inside the host cell, the negative strand viral RNA is replicated by the viral RNA polymerase to form mRNA, which is translated by the host to produce viral proteins. Additional viral RNA molecules are transcribed to produce viral genomic RNA, which assemble with viral proteins to form mature virions. Release of the virions from the host cell is facilitated by viral neuraminidase, which cleaves sialic-acid receptors to allow progeny viruses to make a clean exit when budding from an infected cell.

There are three genetically related influenza viruses, called A, B, and C. The influenza A viruses have different subtypes based on the structure of their hemagglutinin and neuraminidase proteins. There are currently 18 known subtypes of hemagglutinin and 11 known subtypes of neuraminidase. Influenza viruses are serologically characterized by the type of H and N proteins that they possess. Of the nearly 200 different combinations of H and N, only a few, such as the H1N1 strain, are associated with human disease. The influenza viruses A, B, and C make up three of the five major groups of orthomyxoviruses. The differences between the three types of influenza are summarized in Table 12.1.2. The most virulent group is the influenza A viruses, which cause seasonal pandemics of influenza each year. Influenza A virus can infect a variety of animals, including pigs, horses, pigs, and even whales and dolphins. Influenza B virus is less virulent and is sometimes associated with epidemic outbreaks. Influenza C virus generally produces the mildest disease symptoms and is rarely connected with epidemics. Neither influenza B virus nor influenza C virus has significant animal reservoirs.

*Table 12.1.2: The Three Major Groups of Influenza Viruses*

| | Influenza A virus | Influenza B virus | Influenza C virus |
|---|---|---|---|
| Severity | Severe | Moderate | Mild |
| Animal reservoir | Yes | No | No |
| Genome segments | 8 | 8 | 7 |
| Population spread | Epidemic and pandemic | Epidemic | Sporadic |
| Antigenic variation | Shift/drift | Drift | Drift |

Influenza virus infections elicit a strong immune response, particularly to the hemagglutinin protein, which would protect the individual if they encountered the same virus. Unfortunately, the antigenic properties of the virus change relatively rapidly, so new strains are evolving that immune systems previously challenged by influenza virus cannot recognize. When an influenza virus gains a new hemagglutinin or neuraminidase type, it is able to evade the host's immune response and be successfully transmitted, often leading to an epidemic.

There are two mechanisms by which these evolutionary changes may occur. The mechanisms of antigen drift and antigenic shift for influenza virus have been described in Virulence Factors of Bacterial and Viral Pathogens. Of these two genetic processes, it is viruses produced by antigenic shift that have the potential to be extremely virulent because individuals previously infected by other strains are unlikely to produce any protective immune response against these novel variants.

The most lethal influenza pandemic in recorded history occurred from 1918 through 1919. Near the end of World War I, an antigenic shift involving the recombination of avian and human viruses is thought to have produced a new H1N1 virus. This strain rapidly spread worldwide and is commonly claimed to have killed as many as 40 million to 50 million people—more than double the number killed in the war. Although referred to as the Spanish flu, this disease is thought to have originated in the United States. Regardless of its source, the conditions of World War I greatly contributed to the spread of this disease. Crowding, poor sanitation, and rapid mobilization of large numbers of personnel and animals facilitated the dissemination of the new virus once it appeared.

Several of the most important influenza pandemics of modern times have been associated with antigenic shifts. A few of these are summarized in Table 12.1.3.

*Table 12.1.3: Historical Influenza Outbreaks*[4] [5] [6]

| Years | Common Name | Serotype | Estimated Number of Deaths |
|---|---|---|---|
| 1918–1919 | Spanish flu | H1N1 | 20,000,000–40,000,000 |
| 1957–1958 | Asian flu | N2N2 | 1,000,000–2,000,000 |
| 1968–1969 | Hong Kong flu | H3N2 | 1,000,000–3,000,000 |
| 2009–2010 | Swine flu | H1N1/09 | 152,000–575,000 |

Laboratory diagnosis of influenza is typically performed using a variety of RIDTs. These tests are inoculated by point-of-care personnel and give results within 15–20 minutes. Unfortunately, these tests have variable sensitivity and commonly yield false-negative results. Other tests include hemagglutination of erythrocytes (due to hemagglutinin action) or complement fixation. Patient serum antibodies against influenza viruses can also be detected in blood samples. Because influenza is self-limiting disease, diagnosis through these more time-consuming and expensive methods is not typically used.

Three drugs that inhibit influenza neuraminidase activity are available: inhaled zanamivir, oral oseltamivir, and intravenous peramivir. If taken at the onset of symptoms, these drugs can shorten the course of the disease. These drugs are thought to impair the ability of the virus to efficiently exit infected host cells. A more effective means of controlling influenza outbreaks, though, is vaccination. Every year, new influenza vaccines are developed to be effective against the strains expected to be predominant. This is determined in February by a review of the dominant strains around the world from a network of reporting sites; their reports are used to generate a recommendation for the vaccine combination for the following winter in the northern hemisphere. In September, a similar recommendation is made for the winter in the southern hemisphere.[7] These recommendations are used by vaccine manufacturers to formulate each year's vaccine. In most cases, three or four viruses are selected—the two most prevalent influenza A strains and one or two influenza B strains. The chosen strains are typically cultivated in eggs and used to produce either an inactivated or a live attenuated vaccine (e.g., FluMist). For individuals 18 years or older with an allergy to egg products, a recombinant egg-free trivalent vaccine is available. Most of the influenza vaccines over the past decade have had an effectiveness of about 50%.[8]

## Case in Point

**Flu Pandemic**

During the spring of 2013, a new strain of H7N9 influenza was reported in China. A total of 132 people were infected. Of those infected, 44 (33%) died. A genetic analysis of the virus suggested that this strain arose from the reassortment of three different influenza viruses: a domestic duck H7N3 virus, a wild bird H7N9 virus, and a domestic poultry H9N2 virus. The virus was detected in the Chinese domestic bird flocks and contact with this reservoir is thought to have been the primary source of infection. This strain of influenza was not able to spread from person to person. Therefore, the disease did not become a global problem. This case does, though, illustrate the potential threat that influenza still represents. If a strain like the H7N9

virus were to undergo another antigenic shift, it could become more communicable in the human population. With a mortality rate of 33%, such a pandemic would be disastrous. For this reason, organizations like the World Health Organization and the Centers for Disease Control and Prevention keep all known influenza outbreaks under constant surveillance.

**Exercise 12.1.3**

1. Compare the severity of the three types of influenza viruses.
2. Why must new influenza vaccines be developed each year?

*Answer available at the end of this section.*

## Key Concepts and Summary

- Viruses cause respiratory tract infections more frequently than bacteria, and most viral infections lead to mild symptoms.
- The **common cold** can be caused by more than 200 viruses, typically rhinoviruses, coronaviruses, and adenoviruses, transmitted by direct contact, aerosols, or environmental surfaces.
- Due to its ability to rapidly mutate through **antigenic drift** and **antigenic shift**, **influenza** remains an important threat to human health. Two new influenza vaccines are developed annually.

## Footnotes


1. AG L'Huillier et al. "Survival of Rhinoviruses on Human Fingers." *Clinical Microbiology and Infection* 21, no. 4 (2015):381–385.
2. Centers for Disease Control and Prevention. "Estimating Seasonal Influenza-Associated Deaths in the United States: CDC Study Confirms Variability of Flu." 2016. https://www.cdc.gov/flu/about/burden/preliminary-in-season-estimates.htm. Accessed July 6, 2016.
3. ED Belay et al. "Reye's Syndrome in the United States From 1981 Through 1997." *New England Journal of Medicine* 340 no. 18 (1999):1377–1382.
4. CE Mills et al. "Transmissibility of 1918 Pandemic Influenza." *Nature* 432, no. 7019 (2004):904–906.
5. E. Tognotti. "Influenza Pandemics: A Historical Retrospect." *Journal of Infection in Developing Countries* 3, no. 5 (2009):331–334.
6. FS Dawood et al. "Estimated Global Mortality Associated with the First 12 Months of 2009 Pandemic Influenza A H1N1 Virus Circulation: A Modelling Study." *The Lancet Infectious Diseases* 12, no. 9 (2012):687–695.
7. World Health Organization. "WHO Report on Global Surveillance of Epidemic-Prone Infectious Diseases." 2000. http://www.who.int/csr/resources/pub.../Influenza.pdf. Accessed July 6, 2016.
8. Centers of Disease Control and Prevention. "Vaccine Effectiveness - How Well Does the Flu Vaccine Work?" 2016. http://www.cdc.gov/flu/about/qa/vaccineeffect.htm. Accessed July 6, 2016.
9. Y. Huang. "The SARS Epidemic and Its Aftermath in China: A Political Perspective." In *Learning from SARS: Preparing for the Next Disease Outbreak*. Edited by S. Knobler et al. Washington, DC: National Academies Press; 2004. Available at: www.ncbi.nlm.nih.gov/books/NBK92479/
10. Centers for Disease Control and Prevention. "Global Health - Measles, Rubella, and CRS, Eliminating Measles, Rubella & Congenital Rubella Syndrome (CRS) Worldwide." 2015. http://www.cdc.gov/globalhealth/measles/. Accessed July 7, 2016.
11. World Health Organization. "Measles Factsheet." 2016. http://www.who.int/mediacentre/factsheets/fs286/en/. Accessed July 7, 2016.
12. Centers for Disease Control and Prevention. "Measles Cases and Outbreaks." 2016. http://www.cdc.gov/measles/cases-outbreaks.html. Accessed July 7, 2016.
13. Ibid.
14. World Health Organization. "Measles-Rubella Bulletin." Manila, Philippines; Expanded Programme on Immunization Regional Office for the Western Pacific World Health Organization; 9 no. 1 (2015). http://www.wpro.who.int/immunization...vol9issue1.pdf
15. M. Bloch et al. "Vaccination Rates for Every Kindergartener in California." *The New York Times* February 6, 2015. http://www.nytimes.com/interactive/2...-map.html?_r=1. Accessed July 7, 2016.
16. E. Miller et al. "Consequences of Confirmed Maternal Rubella at Successive Stages of Pregnancy." *The Lancet* 320, no. 8302 (1982):781–784.
17. Centers for Disease Control and Prevention. "CDC Media Statement on Newly Discovered Smallpox Specimens." July 8, 2014.

http://www.cdc.gov/media/releases/2014/s0708-nih.html. Accessed on July 7, 2016.
18. Ibid.

## Answers

**Exercise** 12.1.3

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# 12.2: Review Questions

## Multiple Choice

1. Which of the following viruses is not commonly associated with the common cold?
   A. coronavirus
   B. adenovirus
   C. rhinovirus
   D. varicella-zoster virus

*Answer available at the end of this section.*

## Fill in the Blank

2. A(n) _____ is an uncontrolled positive feedback loop between cytokines and leucocytes.

*Answer available at the end of this section.*

3. The slow accumulation of genetic changes to an influenza virus over time is referred to as _____.

*Answer available at the end of this section.*

## Short Answer

4. Since we all have experienced many colds in our lifetime, why are we not resistant to future infections?

## Critical Thinking

5. What role does the common cold have in the rise of antibiotic-resistant strains of bacteria in the United States?
6. Why is it highly unlikely that influenza A virus will ever be eradicated, like the smallpox virus?

## Answers

**Multiple Choice**
D

**Fill in the Blank**
cytokine storm

**Fill in the Blank**
antigenic drift

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# 12: RESPIRATORY SYSTEM INFECTIONS (PART A)

The respiratory tract is one of the main portals of entry into the human body for microbial pathogens. On average, a human takes about 20,000 breaths each day. This roughly corresponds to 10,000 liters, or 10 cubic meters, of air. Suspended within this volume of air are millions of microbes of terrestrial, animal, and human origin—including many potential pathogens. A few of these pathogens will cause relatively mild infections like sore throats and colds. Others, however, are less benign. According to the World Health Organization, respiratory tract infections such as tuberculosis, influenza, and pneumonia were responsible for more than 4 million deaths worldwide in 2012.[1]

## Chapter Outline

12.1: Viral Infections of the Respiratory Tract

12.2: Review Questions

## Footnotes

1. World Health Organization. “The Top Ten Causes of Death.” May 2014. http://www.who.int/mediacentre/factsheets/fs310/en/

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# WEEK 8


## 13: Respiratory System Infections (Part B)

13.1: Viral Infections of the Respiratory Tract

13.2: Review Questions


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# 13.1: Viral Infections of the Respiratory Tract

## SARS and MERS

Severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) are two acute respiratory infections caused by coronaviruses. In both cases, these are thought to be zoonotic infections. Bats and civet cats are thought to have been the reservoirs for SARS; camels seem to be the reservoir for MERS.

SARS originated in southern China in the winter of 2002 and rapidly spread to 37 countries. Within about 1 year, more than 8,000 people experienced influenza-like symptoms and nearly 800 people died. The rapid spread and severity of these infections caused grave concern at the time. However, the outbreak was controlled in 2003 and no further cases of SARS have been recorded since 2004.[9] Signs and symptoms of SARS include high fever, headache, body aches, and cough, and most patients will develop pneumonia.

MERS was first reported in Saudi Arabia in 2013. Although some infected individuals will be asymptomatic or have mild cold-like symptoms, most will develop a high fever, aches, cough and a severe respiratory infection that can progress to pneumonia. As of 2015, over 1,300 people in 27 countries have been infected. About 500 people have died. There are no specific treatments for either MERS or SARS. In addition, no vaccines are currently available. Several recombinant vaccines, however, are being developed.

**Exercise 13.1.5**

1. What is the cause of SARS?
2. What are the signs and symptoms of MERS?

## Viral Respiratory Diseases Causing Skin Rashes

Measles and rubella (German measles) are two important viral diseases often associated with skin rashes. However, their symptoms are systemic, and because their portal of entry is the respiratory tract, they can be considered respiratory infections.

### Measles (Rubeola)

The measles virus (MeV) causes the highly contagious disease measles, also known as rubeola, which is a major cause of childhood mortality worldwide. Although vaccination efforts have greatly reduced the incidence of measles in much of the world, epidemics are still common in unvaccinated populations in certain countries.[10]

The measles virus is a single-stranded, negative-strand RNA virus and, like the influenza virus, it possesses an envelope with spikes of embedded hemagglutinin. The infection is spread by direct contact with infectious secretions or inhalation of airborne droplets spread by breathing, coughing, or sneezing. Measles is initially characterized by a high fever, conjunctivitis, and a sore throat. The virus then moves systemically through the bloodstream and causes a characteristic rash. The measles rash initially forms on the face and later spreads to the extremities. The red, raised macular rash will eventually become confluent and can last for several days. At the same time, extremely high fevers (higher than 40.6 °C [105 °F]) can occur. Another diagnostic sign of measles infections is Koplik's spots, white spots that form on the inner lining of inflamed cheek tissues (Figure 13.1.2).




(a) (b) (c)

Figure 13.1.2: (a) Measles typically presents as a raised macular rash that begins on the face and spreads to the extremities. (b) Koplik's spots on the oral mucosa are also characteristic of measles. (c) A thin-section transmission electron micrograph of a measles virion. (credit a, b, c: modification of work by Centers for Disease Control and Prevention)

Although measles is usually self-limiting, it can lead to pneumonia, encephalitis, and death. In addition, the inhibition of immune system cells by the measles virus predisposes patients to secondary infections. In severe infections with highly virulent strains, measles fatality rates can be as high as 10% to 15%. There were more than 145,000 measles deaths (mostly young children) worldwide in 2013.[11]

The preliminary diagnosis of measles is typically based on the appearance of the rash and Koplik's spots. Hemagglutination inhibition tests and serological tests may be used to confirm measles infections in low-prevalence settings.

There are no effective treatments for measles. Vaccination is widespread in developed countries as part of the measles, mumps, and rubella (MMR) vaccine. As a result, there are typically fewer than 200 cases of measles in the United States annually.[12] When it is seen, it is often associated with children who have not been vaccinated.

Micro Connections

**Preventable Measles Outbreaks**

In December 2014, a measles epidemic began at Disneyland in southern California. Within just 4 months, this outbreak affected 134 people in 24 states.[13] Characterization of the virus suggests that an unidentified infected individual brought the disease to the United States from the Philippines, where a similar virus had sickened more than 58,000 people and killed 110.[14] Measles is highly communicable, and its spread at Disneyland may have been facilitated by the low vaccination rate in some communities in California.[15]

Several factors could conceivably lead to a strong comeback of measles in the U.S. Measles is still an epidemic disease in many locations worldwide. Air travel enables infected individuals to rapidly translocate these infections globally. Compounding this problem, low vaccination rates in some local areas in the United States (such as in Amish communities) provide populations of susceptible hosts for the virus to establish itself. Finally, measles has been a low-prevalence infection in the U.S. for some time. As a consequence, physicians are not as likely to recognize the initial symptoms and make accurate diagnoses. Until vaccination rates become high enough to ensure herd immunity, measles is likely to be an ongoing problem in the United States.

## Rubella (German Measles)

Rubella, or the German measles, is a relatively mild viral disease that produces a rash somewhat like that caused by the measles, even though the two diseases are unrelated. The rubella virus is an enveloped RNA virus that can be found in the respiratory tract. It is transmitted from person to person in aerosols produced by coughing or sneezing. Nearly half of all infected people remain asymptomatic. However, the virus is shed and spread by asymptomatic carriers. Like rubeola, rubella begins with a facial rash that spreads to the extremities (Figure 13.1.3). However, the rash is less intense, shorter lived (2–3 days), not associated with Koplik's spots, and the resulting fever is lower (101 °F [38.3 °C]).

Congenital rubella syndrome is the most severe clinical complication of the German measles. This occurs if a woman is infected

with rubella during pregnancy. The rubella virus is teratogenic, meaning it can cause developmental defects if it crosses the placenta during pregnancy. There is a very high incidence of stillbirth, spontaneous abortion, or congenital birth defects if the mother is infected before 11 weeks of pregnancy and 35% if she is infected between weeks 13–16; after this time the incidence is low.[16] For this reason, prenatal screening for rubella is commonly practiced in the United States. Postnatal infections are usually self-limiting and rarely cause severe complications.

Like measles, the preliminary diagnosis of rubella is based on the patient's history, vaccination records, and the appearance of the rash. The diagnosis can be confirmed by hemagglutinin inhibition assays and a variety of other immunological techniques. There are no antiviral therapies for rubella, but an effective vaccine (MMR) is widely available. Vaccination efforts have essentially eliminated rubella in the United States; fewer than a dozen cases are reported in a typical year.

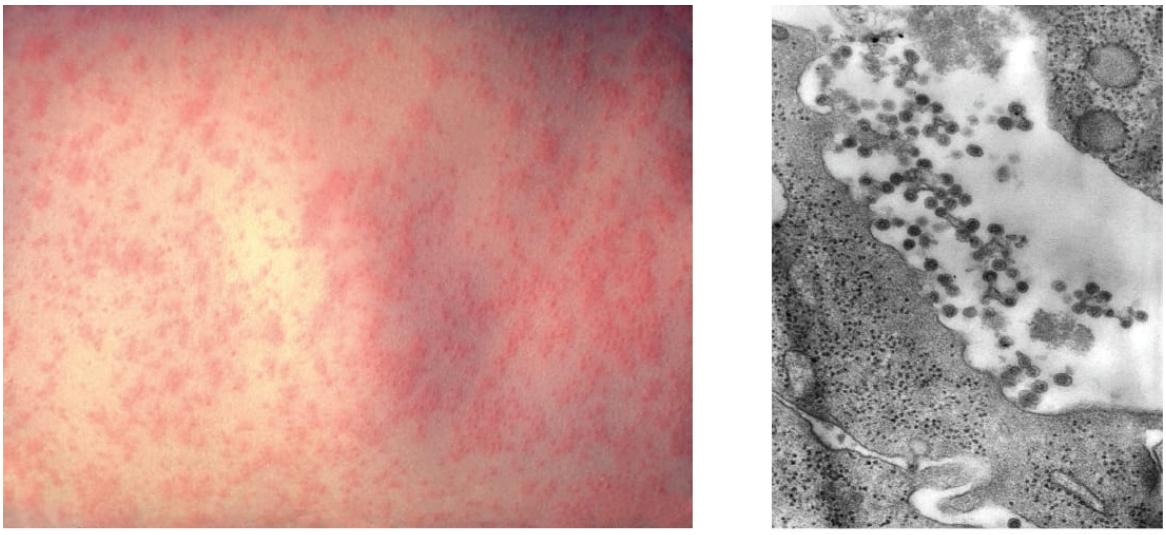



Figure 13.1.3: (a) This photograph shows the appearance of the German measles (rubella) rash. Note that this is less intense than the rash of measles and the lesions are not confluent. (b) This transmission electron micrograph shows rubella virus virions just budding from a host cell. (credit a, b: modification of work by Centers for Disease Control and Prevention)

## Key Concepts and Summary

- **SARS** and **MERS** are acute respiratory infections caused by coronaviruses, and both appear to originate in animals. SARS has not been seen in the human population since 2004 but had a high mortality rate during its outbreak. MERS also has a high mortality rate and continues to appear in human populations.
- **Measles** and **rubella** are highly contagious, systemic infections that gain entry through the respiratory system and cause rashes and fevers. Vaccines are available for both. Measles is the most severe and is responsible for significant mortality around the world.

## Footnotes

1. AG L'Huillier et al. "Survival of Rhinoviruses on Human Fingers." *Clinical Microbiology and Infection* 21, no. 4 (2015):381–385.
2. Centers for Disease Control and Prevention. "Estimating Seasonal Influenza-Associated Deaths in the United States: CDC Study Confirms Variability of Flu." 2016. https://www.cdc.gov/flu/about/burden/preliminary-in-season-estimates.htm. Accessed July 6, 2016.
3. ED Belay et al. "Reye's Syndrome in the United States From 1981 Through 1997." *New England Journal of Medicine* 340 no. 18 (1999):1377–1382.
4. CE Mills et al. "Transmissibility of 1918 Pandemic Influenza." *Nature* 432, no. 7019 (2004):904–906.
5. E. Tognotti. "Influenza Pandemics: A Historical Retrospect." *Journal of Infection in Developing Countries* 3, no. 5 (2009):331–334.
6. FS Dawood et al. "Estimated Global Mortality Associated with the First 12 Months of 2009 Pandemic Influenza A H1N1 Virus Circulation: A Modelling Study." *The Lancet Infectious Diseases* 12, no. 9 (2012):687–695.
7. World Health Organization. "WHO Report on Global Surveillance of Epidemic-Prone Infectious Diseases." 2000.

http://www.who.int/csr/resources/pub.../Influenza.pdf. Accessed July 6, 2016.
8. Centers of Disease Control and Prevention. “Vaccine Effectiveness - How Well Does the Flu Vaccine Work?” 2016. http://www.cdc.gov/flu/about/qa/vaccineeffect.htm. Accessed July 6, 2016.
9. Y. Huang. “The SARS Epidemic and Its Aftermath in China: A Political Perspective.” In *Learning from SARS: Preparing for the Next Disease Outbreak*. Edited by S. Knobler et al. Washington, DC: National Academies Press; 2004. Available at: www.ncbi.nlm.nih.gov/books/NBK92479/
10. Centers for Disease Control and Prevention. “Global Health - Measles, Rubella, and CRS, Eliminating Measles, Rubella & Congenital Rubella Syndrome (CRS) Worldwide.” 2015. http://www.cdc.gov/globalhealth/measles/. Accessed July 7, 2016.
11. World Health Organization. “Measles Factsheet.” 2016. http://www.who.int/mediacentre/factsheets/fs286/en/. Accessed July 7, 2016.
12. Centers for Disease Control and Prevention. “Measles Cases and Outbreaks.” 2016. http://www.cdc.gov/measles/cases-outbreaks.html. Accessed July 7, 2016.
13. Ibid.
14. World Health Organization. “Measles-Rubella Bulletin.” Manila, Philippines; Expanded Programme on Immunization Regional Office for the Western Pacific World Health Organization; 9 no. 1 (2015). http://www.wpro.who.int/immunization...vol9issue1.pdf
15. M. Bloch et al. “Vaccination Rates for Every Kindergartener in California.” *The New York Times* February 6, 2015. http://www.nytimes.com/interactive/2...-map.html?_r=1. Accessed July 7, 2016.
16. E. Miller et al. “Consequences of Confirmed Maternal Rubella at Successive Stages of Pregnancy.” *The Lancet* 320, no. 8302 (1982):781–784.
17. Centers for Disease Control and Prevention. “CDC Media Statement on Newly Discovered Smallpox Specimens.” July 8, 2014. http://www.cdc.gov/media/releases/2014/s0708-nih.html. Accessed on July 7, 2016.
18. Ibid.

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# 13.2: Review Questions

## Multiple Choice

1. Which of the following diseases is not associated with coronavirus infections?
   A. Middle East respiratory syndrome
   B. German measles
   C. the common cold
   D. severe acute respiratory syndrome

*Answer available at the end of this section.*

## Fill in the Blank

2. The _____ virus is responsible for causing German measles.

*Answer available at the end of this section.*

3. The _____ vaccine is effective in controlling both measles and rubella.

*Answer available at the end of this section.*

## Answers

**Multiple Choice**

B

**Fill in the Blank**

rubella

**Fill in the Blank**

MMR

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# 13: RESPIRATORY SYSTEM INFECTIONS (PART B)

At one time, it was thought that antimicrobial drugs and preventive vaccines might hold respiratory infections in check in the developed world, but recent developments suggest otherwise. The rise of multiple-antibiotic resistance in organisms like *Mycobacterium tuberculosis* has rendered many of our modern drugs ineffective. In addition, there has been a recent resurgence in diseases like whooping cough and measles, once-common childhood illnesses made rare by effective vaccines. Despite advances in medicine and public health programs, it is likely that respiratory pathogens will remain formidable adversaries for the foreseeable future.

## Chapter Outline

13.1: Viral Infections of the Respiratory Tract

13.2: Review Questions

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# WEEK 9

## 14: Disease and Epidemiology (Part B)


14.1: The Language of Epidemiologists

14.2: How Diseases Spread

14.3: Global Public Health

14.4: Review Questions


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# 14.1: The Language of Epidemiologists

## Learning Objectives

- Explain the difference between prevalence and incidence of disease
- Distinguish the characteristics of sporadic, endemic, epidemic, and pandemic diseases
- Explain the use of Koch's postulates and their modifications to determine the etiology of disease
- Explain the relationship between epidemiology and public health

## Clinical Focus

**Part 1**

In late November and early December, a hospital in western Florida started to see a spike in the number of cases of acute gastroenteritis-like symptoms. Patients began arriving at the emergency department complaining of excessive bouts of emesis (vomiting) and diarrhea (with no blood in the stool). They also complained of abdominal pain and cramping, and most were severely dehydrated. Alarmed by the number of cases, hospital staff made some calls and learned that other regional hospitals were also seeing 10 to 20 similar cases per day.

- What are some possible causes of this outbreak?
- In what ways could these cases be linked, and how could any suspected links be confirmed?

Jump to the next Clinical Focus box.

The field of epidemiology concerns the geographical distribution and timing of infectious disease occurrences and how they are transmitted and maintained in nature, with the goal of recognizing and controlling outbreaks. The science of epidemiology includes etiology (the study of the causes of disease) and investigation of disease transmission (mechanisms by which a disease is spread).

## Analyzing Disease in a Population

Epidemiological analyses are always carried out with reference to a population, which is the group of individuals that are at risk for the disease or condition. The population can be defined geographically, but if only a portion of the individuals in that area are susceptible, additional criteria may be required. Susceptible individuals may be defined by particular behaviors, such as intravenous drug use, owning particular pets, or membership in an institution, such as a college. Being able to define the population is important because most measures of interest in epidemiology are made with reference to the size of the population.

The state of being diseased is called morbidity. Morbidity in a population can be expressed in a few different ways. Morbidity or total morbidity is expressed in numbers of individuals without reference to the size of the population. The morbidity rate can be expressed as the number of diseased individuals out of a standard number of individuals in the population, such as 100,000, or as a percent of the population.

There are two aspects of morbidity that are relevant to an epidemiologist: a disease's prevalence and its incidence. Prevalence is the number, or proportion, of individuals with a particular illness in a given population at a point in time. For example, the Centers for Disease Control and Prevention (CDC) estimated that in 2012, there were about 1.2 million people 13 years and older with an active human immunodeficiency virus (HIV) infection. Expressed as a proportion, or rate, this is a prevalence of 467 infected persons per 100,000 in the population.[1] On the other hand, incidence is the number or proportion of *new* cases in a period of time. For the same year and population, the CDC estimates that there were 43,165 newly diagnosed cases of HIV infection, which is an incidence of 13.7 new cases per 100,000 in the population.[2] The relationship between incidence and prevalence can be seen in Figure 14.1.1. For a chronic disease like HIV infection, prevalence will generally be higher than incidence because it represents the cumulative number of new cases over many years minus the number of cases that are no longer active (e.g., because the patient died or was cured).

In addition to morbidity rates, the incidence and prevalence of mortality (death) may also be reported. A mortality ratecan be expressed as the percentage of the population that has died from a disease or as the number of deaths per 100,000 persons (or other suitable standard number).

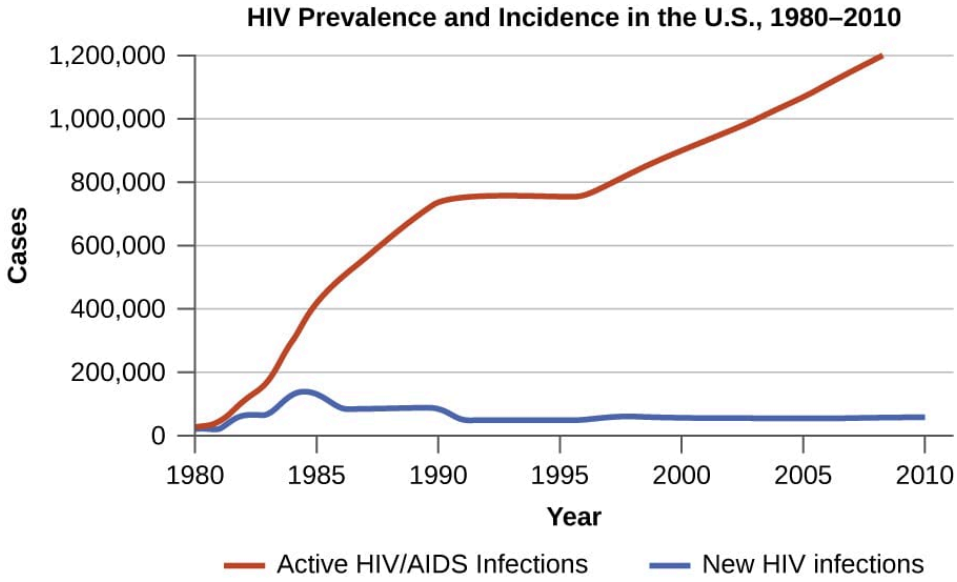



Figure 14.1.1: This graph compares the incidence of HIV (the number of new cases reported each year) with the prevalence (the total number of cases each year). Prevalence and incidence can also be expressed as a rate or proportion for a given population.

**Exercise 14.1.1**

1. Explain the difference between incidence and prevalence.
2. Describe how morbidity and mortality rates are expressed.

## Patterns of Incidence

Diseases that are seen only occasionally, and usually without geographic concentration, are called sporadic diseases. Examples of sporadic diseases include tetanus, rabies, and plague. In the United States, *Clostridium tetani*, the bacterium that causes tetanus, is ubiquitous in the soil environment, but incidences of infection occur only rarely and in scattered locations because most individuals are vaccinated, clean wounds appropriately, or are only rarely in a situation that would cause infection.[3] Likewise in the United States there are a few scattered cases of plague each year, usually contracted from rodents in rural areas in the western states.[4]

Diseases that are constantly present (often at a low level) in a population within a particular geographic region are called endemic diseases. For example, malaria is endemic to some regions of Brazil, but is not endemic to the United States.

Diseases for which a larger than expected number of cases occurs in a short time within a geographic region are called epidemic diseases. Influenza is a good example of a commonly epidemic disease. Incidence patterns of influenza tend to rise each winter in the northern hemisphere. These seasonal increases are expected, so it would not be accurate to say that influenza is epidemic every winter; however, some winters have an usually large number of seasonal influenza cases in particular regions, and such situations would qualify as epidemics (Figure 14.1.2 and Figure 14.1.3).

An epidemic disease signals the breakdown of an equilibrium in disease frequency, often resulting from some change in environmental conditions or in the population. In the case of influenza, the disruption can be due to antigenic shift or drift (see Virulence Factors of Bacterial and Viral Pathogens), which allows influenza virus strains to circumvent the acquired immunity of their human hosts.

An epidemic that occurs on a worldwide scale is called a pandemic disease. For example, HIV/AIDS is a pandemic disease and novel influenza virus strains often become pandemic.

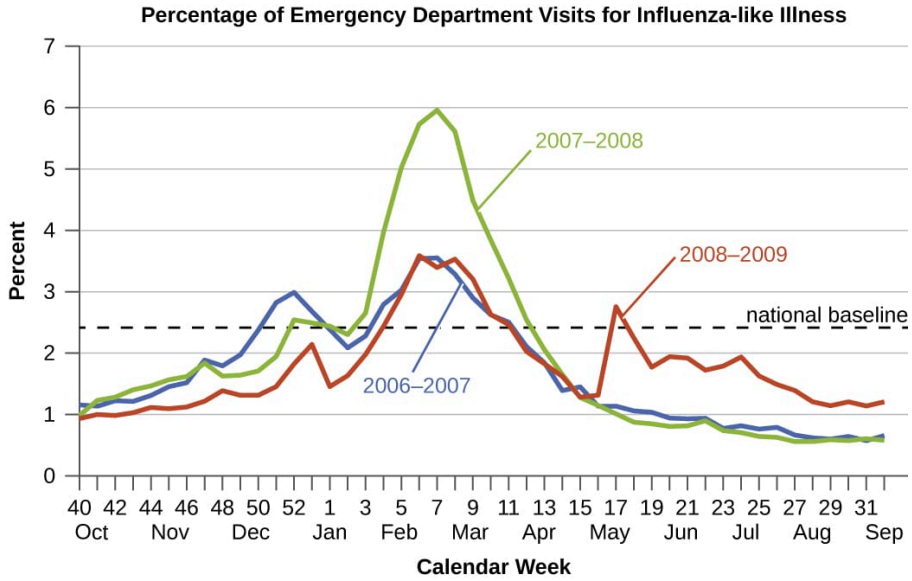



Figure 14.1.2: The 2007–2008 influenza season in the United States saw much higher than normal numbers of visits to emergency departments for influenza-like symptoms as compared to the previous and the following years. (credit: modification of work by Centers for Disease Control and Prevention)

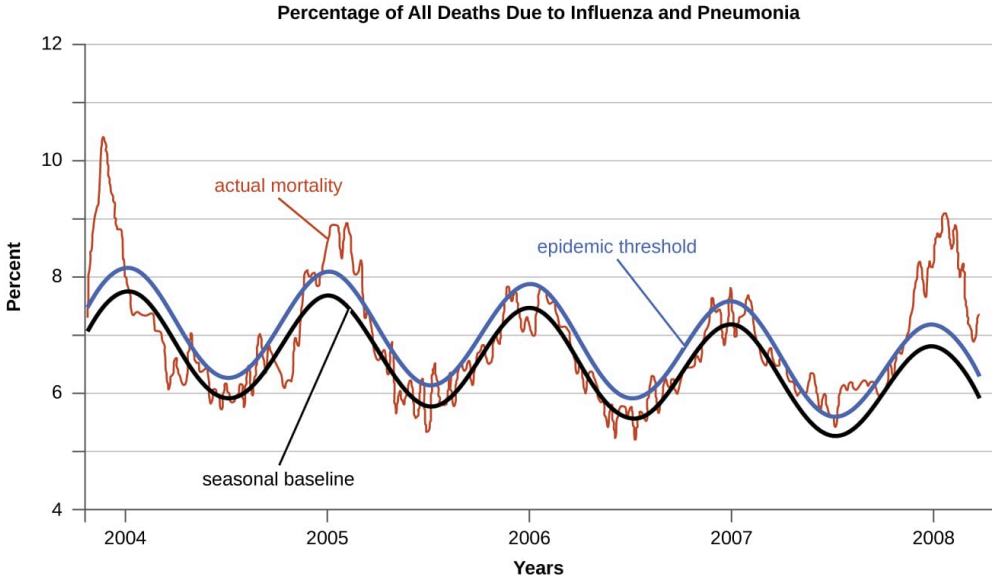



Figure 14.1.3: The seasonal epidemic threshold (blue curve) is set by the CDC-based data from the previous five years. When actual mortality rates exceed this threshold, a disease is considered to be epidemic. As this graph shows, pneumonia- and influenza-related mortality saw pronounced epidemics during the winters of 2003–2004, 2005, and 2008. (credit: modification of work by Centers for Disease Control and Prevention)

## Exercise 14.1.2

1. Explain the difference between sporadic and endemic disease.
2. Explain the difference between endemic and epidemic disease.

## Clinical Focus

**Part 2**

Hospital physicians suspected that some type of food poisoning was to blame for the sudden post-Thanksgiving outbreak of gastroenteritis in western Florida. Over a two-week period, 254 cases were observed, but by the end of the first week of December, the epidemic ceased just as quickly as it had started. Suspecting a link between the cases based on the localized nature of the outbreak, hospitals handed over their medical records to the regional public health office for study.

Laboratory testing of stool samples had indicated that the infections were caused by *Salmonella* bacteria. Patients ranged from children as young as three to seniors in their late eighties. Cases were nearly evenly split between males and females. Across the region, there had been three confirmed deaths in the outbreak, all due to severe dehydration. In each of the fatal cases, the patients had not sought medical care until their symptoms were severe; also, all of the deceased had preexisting medical conditions such as congestive heart failure, diabetes, or high blood pressure.

After reviewing the medical records, epidemiologists with the public health office decided to conduct interviews with a randomly selected sample of patients.

- What conclusions, if any, can be drawn from the medical records?
- What would epidemiologists hope to learn by interviewing patients? What kinds of questions might they ask?

Jump to the next Clinical Focus box. Go back to the previous Clinical Focus box.

## Etiology

When studying an epidemic, an epidemiologist's first task is to determinate the cause of the disease, called the etiologic agent or causative agent. Connecting a disease to a specific pathogen can be challenging because of the extra effort typically required to demonstrate direct causation as opposed to a simple association. It is not enough to observe an association between a disease and a suspected pathogen; controlled experiments are needed to eliminate other possible causes. In addition, pathogens are typically difficult to detect when there is no immediate clue as to what is causing the outbreak. Signs and symptoms of disease are also commonly nonspecific, meaning that many different agents can give rise to the same set of signs and symptoms. This complicates diagnosis even when a causative agent is familiar to scientists.

Robert Koch was the first scientist to specifically demonstrate the causative agent of a disease (anthrax) in the late 1800s. Koch developed four criteria, now known as Koch's postulates, which had to be met in order to positively link a disease with a pathogenic microbe. Without Koch's postulates, the Golden Age of Microbiology would not have occurred. Between 1876 and 1905, many common diseases were linked with their etiologic agents, including cholera, diphtheria, gonorrhea, meningitis, plague, syphilis, tetanus, and tuberculosis. Today, we use the molecular Koch's postulates, a variation of Koch's original postulates that can be used to establish a link between the disease state and virulence traits unique to a pathogenic strain of a microbe. Koch's original postulates and molecular Koch's postulates were described in more detail in How Pathogens Cause Disease.

**Exercise 14.1.3**

List some challenges to determining the causative agent of a disease outbreak.

## The Role of Public Health Organizations

The main national public health agency in the United States is the Centers for Disease Control and Prevention (CDC), an agency of the Department of Health and Human Services. The CDC is charged with protecting the public from disease and injury. One way that the CDC carries out this mission is by overseeing the National Notifiable Disease Surveillance System (NNDSS) in cooperation with regional, state, and territorial public health departments. The NNDSS monitors diseases considered to be of public health importance on a national scale. Such diseases are called notifiable diseases or reportable diseases because all cases must be reported to the CDC. A physician treating a patient with a notifiable disease is legally required to submit a report on the case. Notifiable diseases include HIV infection, measles, West Nile virus infections, and many others. Some states have their own lists of notifiable diseases that include diseases beyond those on the CDC's list.

Notifiable diseases are tracked by epidemiological studies and the data is used to inform health-care providers and the public about possible risks. The CDC publishes the *Morbidity and Mortality Weekly Report* (*MMWR*), which provides physicians and health-care workers with updates on public health issues and the latest data pertaining to notifiable diseases. Table 14.1.1 is an

example of the kind of data contained in the *MMWR*.

*Table 14.1.1: Incidence of Four Notifiable Diseases in the United States, Week Ending January 2, 2016*

| Disease | Current Week (Jan 2, 2016) | Median of Previous 52 Weeks | Maximum of Previous 52 Weeks | Cumulative Cases 2015 |
|---|---|---|---|---|
| Campylobacteriosis | 406 | 869 | 1,385 | 46,618 |
| *Chlamydia trachomatis* infection | 11,024 | 28,562 | 31,089 | 1,425,303 |
| Giardiasis | 115 | 230 | 335 | 11,870 |
| Gonorrhea | 3,207 | 7,155 | 8,283 | 369,926 |

**Link to Learning**

The current *Morbidity and Mortality Weekly Report* is available online.

**Exercise 14.1.4**

Describe how health agencies obtain data about the incidence of diseases of public health importance.

## Key Concepts and Summary

- **Epidemiology** is the science underlying public health.
- **Morbidity** means being in a state of illness, whereas **mortality** refers to death; both **morbidity rates** and **mortality rates** are of interest to epidemiologists.
- **Incidence** is the number of new cases (morbidity or mortality), usually expressed as a proportion, during a specified time period; **prevalence** is the total number affected in the population, again usually expressed as a proportion.
- **Sporadic diseases** only occur rarely and largely without a geographic focus. **Endemic diseases** occur at a constant (and often low) level within a population. **Epidemic diseases** and **pandemic diseases** occur when an outbreak occurs on a significantly larger than expected level, either locally or globally, respectively.
- **Koch's postulates** specify the procedure for confirming a particular pathogen as the etiologic agent of a particular disease. Koch's postulates have limitations in application if the microbe cannot be isolated and cultured or if there is no animal host for the microbe. In this case, molecular Koch's postulates would be utilized.
- In the United States, the **Centers for Disease Control and Prevention** monitors **notifiable diseases** and publishes weekly updates in the *Morbidity and Mortality Weekly Report*.

## Footnotes


1. H. Irene Hall, Qian An, Tian Tang, Ruiguang Song, Mi Chen, Timothy Green, and Jian Kang. "Prevalence of Diagnosed and Undiagnosed HIV Infection—United States, 2008–2012." *Morbidity and Mortality Weekly Report* 64, no. 24 (2015): 657–662.
2. Centers for Disease Control and Prevention. "Diagnoses of HIV Infection in the United States and Dependent Areas, 2014." *HIV Surveillance Report* 26 (2015).
3. Centers for Disease Control and Prevention. "Tetanus Surveillance—United States, 2001–2008." *Morbidity and Mortality Weekly Report* 60, no. 12 (2011): 365.
4. Centers for Disease Control and Prevention. "Plague in the United States." 2015. http://www.cdc.gov/plague/maps. Accessed June 1, 2016.



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# 14.2: How Diseases Spread

**Learning Objectives**

- Describe the different types of disease reservoirs
- Compare contact, vector, and vehicle modes of transmission
- Identify important disease vectors
- Explain the prevalence of nosocomial infections

Understanding how infectious pathogens spread is critical to preventing infectious disease. Many pathogens require a living host to survive, while others may be able to persist in a dormant state outside of a living host. But having infected one host, all pathogens must also have a mechanism of transfer from one host to another or they will die when their host dies. Pathogens often have elaborate adaptations to exploit host biology, behavior, and ecology to live in and move between hosts. Hosts have evolved defenses against pathogens, but because their rates of evolution are typically slower than their pathogens (because their generation times are longer), hosts are usually at an evolutionary disadvantage. This section will explore where pathogens survive—both inside and outside hosts—and some of the many ways they move from one host to another.

## Reservoirs and Carriers

For pathogens to persist over long periods of time they require reservoirs where they normally reside. Reservoirs can be living organisms or nonliving sites. Nonliving reservoirs can include soil and water in the environment. These may naturally harbor the organism because it may grow in that environment. These environments may also become contaminated with pathogens in human feces, pathogens shed by intermediate hosts, or pathogens contained in the remains of intermediate hosts.

Pathogens may have mechanisms of dormancy or resilience that allow them to survive (but typically not to reproduce) for varying periods of time in nonliving environments. For example, *Clostridium tetani* survives in the soil and in the presence of oxygen as a resistant endospore. Although many viruses are soon destroyed once in contact with air, water, or other non-physiological conditions, certain types are capable of persisting outside of a living cell for varying amounts of time. For example, a study that looked at the ability of influenza viruses to infect a cell culture after varying amounts of time on a banknote showed survival times from 48 hours to 17 days, depending on how they were deposited on the banknote.[1] On the other hand, cold-causing rhinoviruses are somewhat fragile, typically surviving less than a day outside of physiological fluids.

A human acting as a reservoir of a pathogen may or may not be capable of transmitting the pathogen, depending on the stage of infection and the pathogen. To help prevent the spread of disease among school children, the CDC has developed guidelines based on the risk of transmission during the course of the disease. For example, children with chickenpox are considered contagious for five days from the start of the rash, whereas children with most gastrointestinal illnesses should be kept home for 24 hours after the symptoms disappear.

An individual capable of transmitting a pathogen without displaying symptoms is referred to as a carrier. A passive carrier is contaminated with the pathogen and can mechanically transmit it to another host; however, a passive carrier is not infected. For example, a health-care professional who fails to wash his hands after seeing a patient harboring an infectious agent could become a passive carrier, transmitting the pathogen to another patient who becomes infected.

By contrast, an active carrier is an infected individual who can transmit the disease to others. An active carrier may or may not exhibit signs or symptoms of infection. For example, active carriers may transmit the disease during the incubation period (before they show signs and symptoms) or the period of convalescence (after symptoms have subsided). Active carriers who do not present signs or symptoms of disease despite infection are called asymptomatic carriers. Pathogens such as hepatitis B virus, herpes simplex virus, and HIV are frequently transmitted by asymptomatic carriers. Mary Mallon, better known as Typhoid Mary, is a famous historical example of an asymptomatic carrier. An Irish immigrant, Mallon worked as a cook for households in and around New York City between 1900 and 1915. In each household, the residents developed typhoid fever (caused by *Salmonella typhi*) a few weeks after Mallon started working. Later investigations determined that Mallon was responsible for at least 122 cases of typhoid fever, five of which were fatal.[2] See Eye on Ethics: Typhoid Mary for more about the Mallon case.

A pathogen may have more than one living reservoir. In zoonotic diseases, animals act as reservoirs of human disease and transmit the infectious agent to humans through direct or indirect contact. In some cases, the disease also affects the animal, but in other cases the animal is asymptomatic.

In parasitic infections, the parasite's preferred host is called the definitive host. In parasites with complex life cycles, the definitive host is the host in which the parasite reaches sexual maturity. Some parasites may also infect one or more intermediate hosts in which the parasite goes through several immature life cycle stages or reproduces asexually.

**Link to Learning**

George Soper, the sanitary engineer who traced the typhoid outbreak to Mary Mallon, gives an account of his investigation, an example of descriptive epidemiology, in "The Curious Career of Typhoid Mary."

**Exercise 14.2.1**

1. List some nonliving reservoirs for pathogens.
2. Explain the difference between a passive carrier and an active carrier.

# Transmission

Regardless of the reservoir, transmission must occur for an infection to spread. First, transmission from the reservoir to the individual must occur. Then, the individual must transmit the infectious agent to other susceptible individuals, either directly or indirectly. Pathogenic microorganisms employ diverse transmission mechanisms.

## Contact Transmission

Contact transmission includes direct contact or indirect contact. Person-to-person transmission is a form of direct contact transmission. Here the agent is transmitted by physical contact between two individuals (Figure 14.2.1) through actions such as touching, kissing, sexual intercourse, or droplet sprays. Direct contact can be categorized as vertical, horizontal, or droplet transmission. Vertical direct contact transmission occurs when pathogens are transmitted from mother to child during pregnancy, birth, or breastfeeding. Other kinds of direct contact transmission are called horizontal direct contact transmission. Often, contact between mucous membranes is required for entry of the pathogen into the new host, although skin-to-skin contact can lead to mucous membrane contact if the new host subsequently touches a mucous membrane. Contact transmission may also be site-specific; for example, some diseases can be transmitted by sexual contact but not by other forms of contact.

When an individual coughs or sneezes, small droplets of mucus that may contain pathogens are ejected. This leads to direct droplet transmission, which refers to droplet transmission of a pathogen to a new host over distances of one meter or less. A wide variety of diseases are transmitted by droplets, including influenza and many forms of pneumonia. Transmission over distances greater than one meter is called airborne transmission.

Indirect contact transmission involves inanimate objects called fomites that become contaminated by pathogens from an infected individual or reservoir (Figure 14.2.2). For example, an individual with the common cold may sneeze, causing droplets to land on a fomite such as a tablecloth or carpet, or the individual may wipe her nose and then transfer mucus to a fomite such as a doorknob or towel. Transmission occurs indirectly when a new susceptible host later touches the fomite and transfers the contaminated material to a susceptible portal of entry. Fomites can also include objects used in clinical settings that are not properly sterilized, such as syringes, needles, catheters, and surgical equipment. Pathogens transmitted indirectly via such fomites are a major cause of healthcare-associated infections (see Controlling Microbial Growth).



Figure 14.2.1: Direct contact transmission of pathogens can occur through physical contact. Many pathogens require contact with a mucous membrane to enter the body, but the host may transfer the pathogen from another point of contact (e.g., hand) to a mucous membrane (e.g., mouth or eye). (credit left: modification of work by Lisa Doehnert)




Figure 14.2.2: Fomites are nonliving objects that facilitate the indirect transmission of pathogens. Contaminated doorknobs, towels, and syringes are all common examples of fomites. (credit left: modification of work by Kate Ter Haar; credit middle: modification of work by Vernon Swanepoel; credit right: modification of work by "Zaldylmg"/Flickr)

## Vehicle Transmission

The term vehicle transmission refers to the transmission of pathogens through vehicles such as water, food, and air. Water contamination through poor sanitation methods leads to waterborne transmission of disease. Waterborne disease remains a serious problem in many regions throughout the world. The World Health Organization (WHO) estimates that contaminated drinking water is responsible for more than 500,000 deaths each year.[3] Similarly, food contaminated through poor handling or storage can lead to foodborne transmission of disease (Figure 14.2.3).

Dust and fine particles known as aerosols, which can float in the air, can carry pathogens and facilitate the airborne transmission of disease. For example, dust particles are the dominant mode of transmission of hantavirus to humans. Hantavirus is found in mouse feces, urine, and saliva, but when these substances dry, they can disintegrate into fine particles that can become airborne when disturbed; inhalation of these particles can lead to a serious and sometimes fatal respiratory infection.

Although droplet transmission over short distances is considered contact transmission as discussed above, longer distance transmission of droplets through the air is considered vehicle transmission. Unlike larger particles that drop quickly out of the air column, fine mucus droplets produced by coughs or sneezes can remain suspended for long periods of time, traveling considerable distances. In certain conditions, droplets desiccate quickly to produce a droplet nucleus that is capable of transmitting pathogens; air temperature and humidity can have an impact on effectiveness of airborne transmission.

Tuberculosis is often transmitted via airborne transmission when the causative agent, *Mycobacterium tuberculosis*, is released in small particles with coughs. Because tuberculosis requires as few as 10 microbes to initiate a new infection, patients with tuberculosis must be treated in rooms equipped with special ventilation, and anyone entering the room should wear a mask.



Figure 14.2.3: Food is an important vehicle of transmission for pathogens, especially of the gastrointestinal and upper respiratory systems. Notice the glass shield above the food trays, designed to prevent pathogens ejected in coughs and sneezes from entering the food. (credit: Fort George G. Meade Public Affairs Office)

Clinical Focus

**Resolution**

After identifying the source of the contaminated turduckens, the Florida public health office notified the CDC, which requested an expedited inspection of the facility by state inspectors. Inspectors found that a machine used to process the chicken was contaminated with *Salmonella* as a result of substandard cleaning protocols. Inspectors also found that the process of stuffing and packaging the turduckens prior to refrigeration allowed the meat to remain at temperatures conducive to bacterial growth for too long. The contamination and the delayed refrigeration led to vehicle (food) transmission of the bacteria in turduckens.

Based on these findings, the plant was shut down for a full and thorough decontamination. All turduckens produced in the plant were recalled and pulled from store shelves ahead of the December holiday season, preventing further outbreaks.

Go back to the previous Clinical Focus Box.

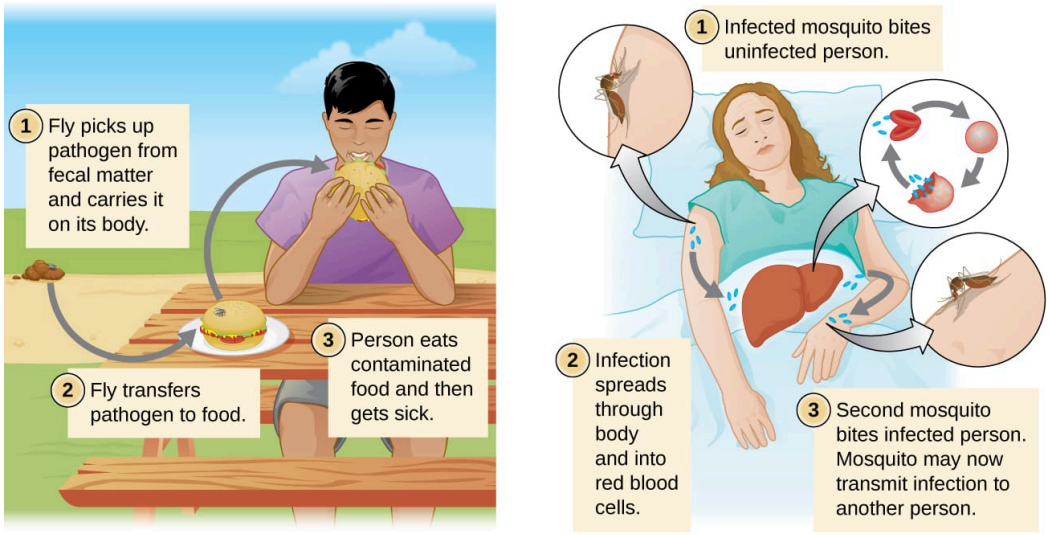
## Vector Transmission

Diseases can also be transmitted by a mechanical or biological vector, an animal (typically an arthropod) that carries the disease from one host to another. Mechanical transmission is facilitated by a mechanical vector, an animal that carries a pathogen from one host to another without being infected itself. For example, a fly may land on fecal matter and later transmit bacteria from the feces to food that it lands on; a human eating the food may then become infected by the bacteria, resulting in a case of diarrhea or dysentery (Figure 14.2.4).

Biological transmission occurs when the pathogen reproduces within a biological vector that transmits the pathogen from one host to another (Figure 14.2.4). Arthropods are the main vectors responsible for biological transmission (Figure 14.2.5). Most arthropod vectors transmit the pathogen by biting the host, creating a wound that serves as a portal of entry. The pathogen may go through part of its reproductive cycle in the gut or salivary glands of the arthropod to facilitate its transmission through the bite. For example, hemipterans (called “kissing bugs” or “assassin bugs”) transmit Chagas disease to humans by defecating when they bite, after which the human scratches or rubs the infected feces into a mucous membrane or break in the skin.

Biological insect vectors include mosquitoes, which transmit malaria and other diseases, and lice, which transmit typhus. Other arthropod vectors can include arachnids, primarily ticks, which transmit Lyme disease and other diseases, and mites, which transmit scrub typhus and rickettsial pox. Biological transmission, because it involves survival and reproduction within a

parasitized vector, complicates the biology of the pathogen and its transmission. There are also important non-arthropod vectors of disease, including mammals and birds. Various species of mammals can transmit rabies to humans, usually by means of a bite that transmits the rabies virus. Chickens and other domestic poultry can transmit avian influenza to humans through direct or indirect contact with avian influenza virus A shed in the birds' saliva, mucous, and feces.




(a) (b)

Figure 14.2.4: (a) A mechanical vector carries a pathogen on its body from one host to another, not as an infection. (b) A biological vector carries a pathogen from one host to another after becoming infected itself.

**Common Arthropod Vectors and Select Pathogens**

| Vector | Species | Pathogen | Disease |
|---|---|---|---|
| Black fly | *Simulium* spp. | *Onchocerca volvulus* | Onchocerciasis (river blindness) |
| Flea | *Xenopsylla cheopis* | *Rickettsia typhi* | Murine typhus |
| | | *Yersinia pestis* | Plague |
| Kissing bug | *Triatoma* spp. | *Trypanosoma cruzi* | Chagas disease |
| Louse | *Pediculus humanus humanus* | *Bartonella quintana* | Trench fever |
| | | *Borrelia recurrentis* | Relapsing fever |
| | | *Rickettsia prowazekii* | Typhus |
| Mite (chigger) | *Leptotrombidium* spp. | *Orientia tsutsugamushi* | Scrub typhus |
| | *Liponyssoides sanguineus* | *Rickettsia akari* | Rickettsialpox |
| Mosquito | *Aedes* spp., *Haemagogus* spp. | *Yellow fever virus* | Yellow fever |
| | *Anopheles* spp. | *Plasmodium falciparum* | Malaria |
| | *Culex pipiens* | *West Nile virus* | West Nile disease |
| Sand fly | *Phlebotomus* spp. | *Leishmania* spp. | Leishmaniasis |
| Tick | *Ixodes* spp. | *Borrelia* spp. | Lyme disease |
| | *Dermacentor* spp. and others | *Rickettsia rickettsii* | Rocky Mountain spotted fever |
| Tsetse fly | *Glossina* spp. | *Trypanosoma brucei* | African trypanosomiasis (sleeping sickness) |

Figure 14.2.5: (credit "Black fly", "Tick", "Tsetse fly": modification of work by USDA; credit: "Flea": modification of work by Centers for Disease Control and Prevention; credit: "Louse", "Mosquito", "Sand fly": modification of work by James Gathany, Centers for Disease Control and Prevention; credit "Kissing bug": modification of work by Glenn Seplak; credit "Mite": modification of work by Michael Wunderli)

## Exercise 14.2.2

1. Describe how diseases can be transmitted through the air.
2. Explain the difference between a mechanical vector and a biological vector.

Eye on Ethics

**Using GMOs to Stop the Spread of Zika**

In 2016, an epidemic of the Zika virus was linked to a high incidence of birth defects in South America and Central America. As winter turned to spring in the northern hemisphere, health officials correctly predicted the virus would spread to North America, coinciding with the breeding season of its major vector, the *Aedes aegypti* mosquito.

The range of the *A. aegypti* mosquito extends well into the southern United States (Figure 14.2.6). Because these same mosquitoes serve as vectors for other problematic diseases (dengue fever, yellow fever, and others), various methods of mosquito control have been proposed as solutions. Chemical pesticides have been used effectively in the past, and are likely to be used again; but because chemical pesticides can have negative impacts on the environment, some scientists have proposed an alternative that involves genetically engineering *A. aegypti* so that it cannot reproduce. This method, however, has been the subject of some controversy.

One method that has worked in the past to control pests, with little apparent downside, has been sterile male introductions. This method controlled the screw-worm fly pest in the southwest United States and fruit fly pests of fruit crops. In this method, males of the target species are reared in the lab, sterilized with radiation, and released into the environment where they mate with wild females, who subsequently bear no live offspring. Repeated releases shrink the pest population.

A similar method, taking advantage of recombinant DNA technology,[4] introduces a dominant lethal allele into male mosquitoes that is suppressed in the presence of tetracycline (an antibiotic) during laboratory rearing. The males are released into the environment and mate with female mosquitoes. Unlike the sterile male method, these matings produce offspring, but they die as larvae from the lethal gene in the absence of tetracycline in the environment. As of 2016, this method has yet to be implemented in the United States, but a UK company tested the method in Piracicaba, Brazil, and found an 82% reduction in wild *A. aegypti* larvae and a 91% reduction in dengue cases in the treated area.[5] In August 2016, amid news of Zika infections in several Florida communities, the FDA gave the UK company permission to test this same mosquito control method in Key West, Florida, pending compliance with local and state regulations and a referendum in the affected communities.

The use of genetically modified organisms (GMOs) to control a disease vector has its advocates as well as its opponents. In theory, the system could be used to drive the *A. aegypti* mosquito extinct—a noble goal according to some, given the damage they do to human populations.[6] But opponents of the idea are concerned that the gene could escape the species boundary of *A. aegypti* and cause problems in other species, leading to unforeseen ecological consequences. Opponents are also wary of the program because it is being administered by a for-profit corporation, creating the potential for conflicts of interest that would have to be tightly regulated; and it is not clear how any unintended consequences of the program could be reversed.

There are other epidemiological considerations as well. *Aedes aegypti* is apparently not the only vector for the Zika virus. *Aedes albopictus*, the Asian tiger mosquito, is also a vector for the Zika virus.[7] *A. albopictus* is now widespread around the planet including much of the United States (Figure 14.2.6). Many other mosquitoes have been found to harbor Zika virus, though their capacity to act as vectors is unknown.[8] Genetically modified strains of *A. aegypti* will not control the other species of vectors. Finally, the Zika virus can apparently be transmitted sexually between human hosts, from mother to child, and possibly through blood transfusion. All of these factors must be considered in any approach to controlling the spread of the virus.

Clearly there are risks and unknowns involved in conducting an open-environment experiment of an as-yet poorly understood technology. But allowing the Zika virus to spread unchecked is also risky. Does the threat of a Zika epidemic justify the ecological risk of genetically engineering mosquitos? Are current methods of mosquito control sufficiently ineffective or harmful that we need to try untested alternatives? These are the questions being put to public health officials now.

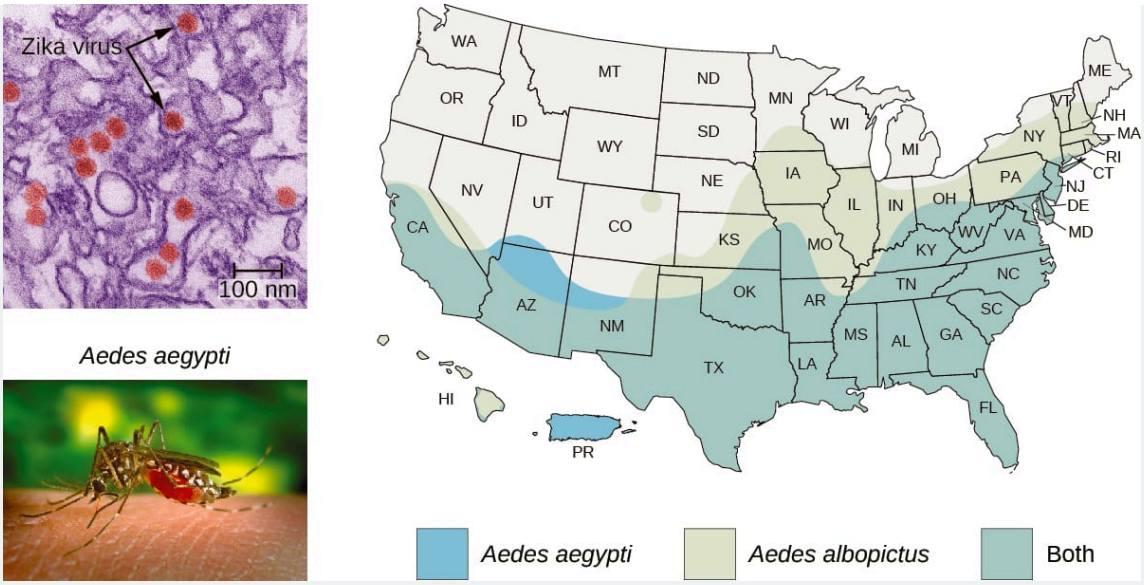



Figure 14.2.6: The Zika virus is an enveloped virus transmitted by mosquitoes, especially *Aedes aegypti.* The range of this mosquito includes much of the United States, from the Southwest and Southeast to as far north as the Mid-Atlantic. The range of *A. albopictus*, another vector, extends even farther north to New England and parts of the Midwest. (credit micrograph: modification of work by Cynthia Goldsmith, Centers for Disease Control and Prevention; credit photo: modification of work by James Gathany, Centers for Disease Control and Prevention; credit map: modification of work by Centers for Disease Control and Prevention)

## Quarantining

Individuals suspected or known to have been exposed to certain contagious pathogens may be quarantined, or isolated to prevent transmission of the disease to others. Hospitals and other health-care facilities generally set up special wards to isolate patients with particularly hazardous diseases such as tuberculosis or Ebola (Figure 14.2.7). Depending on the setting, these wards may be equipped with special air-handling methods, and personnel may implement special protocols to limit the risk of transmission, such as personal protective equipment or the use of chemical disinfectant sprays upon entry and exit of medical personnel.

The duration of the quarantine depends on factors such as the incubation period of the disease and the evidence suggestive of an infection. The patient may be released if signs and symptoms fail to materialize when expected or if preventive treatment can be administered in order to limit the risk of transmission. If the infection is confirmed, the patient may be compelled to remain in isolation until the disease is no longer considered contagious.

In the United States, public health authorities may only quarantine patients for certain diseases, such as cholera, diphtheria, infectious tuberculosis, and strains of influenza capable of causing a pandemic. Individuals entering the United States or moving between states may be quarantined by the CDC if they are suspected of having been exposed to one of these diseases. Although the CDC routinely monitors entry points to the United States for crew or passengers displaying illness, quarantine is rarely implemented.



(a) (b)

Figure 14.2.7: (a) The Aeromedical Biological Containment System (ABCS) is a module designed by the CDC and Department of Defense specifically for transporting highly contagious patients by air. (b) An isolation ward for Ebola patients in Lagos, Nigeria. (credit a: modification of work by Centers for Disease Control and Prevention; credit b: modification of work by CDC Global)

## Healthcare-Associated (Nosocomial) Infections

Hospitals, retirement homes, and prisons attract the attention of epidemiologists because these settings are associated with increased incidence of certain diseases. Higher rates of transmission may be caused by characteristics of the environment itself, characteristics of the population, or both. Consequently, special efforts must be taken to limit the risks of infection in these settings.

Infections acquired in health-care facilities, including hospitals, are called nosocomial infections or healthcare-associated infections (HAI). HAIs are often connected with surgery or other invasive procedures that provide the pathogen with access to the portal of infection. For an infection to be classified as an HAI, the patient must have been admitted to the health-care facility for a reason other than the infection. In these settings, patients suffering from primary disease are often afflicted with compromised immunity and are more susceptible to secondary infection and opportunistic pathogens.

In 2011, more than 720,000 HAIs occurred in hospitals in the United States, according to the CDC. About 22% of these HAIs occurred at a surgical site, and cases of pneumonia accounted for another 22%; urinary tract infections accounted for an additional 13%, and primary bloodstream infections 10%.[9] Such HAIs often occur when pathogens are introduced to patients' bodies through contaminated surgical or medical equipment, such as catheters and respiratory ventilators. Health-care facilities seek to limit nosocomial infections through training and hygiene protocols such as those described in Control of Microbial Growth.

**Exercise 14.2.3**

Give some reasons why HAIs occur.

## Key Concepts and Summary

- **Reservoirs** of human disease can include the human and animal populations, soil, water, and inanimate objects or materials.
- **Contact transmission** can be **direct** or **indirect** through physical contact with either an infected host (direct) or contact with a fomite that an infected host has made contact with previously (indirect).
- Vector transmission occurs when a living organism carries an infectious agent on its body (**mechanical**) or as an infection host itself (**biological**), to a new host.
- **Vehicle transmission** occurs when a substance, such as soil, water, or air, carries an infectious agent to a new host.

- **Healthcare-associated infections (HAI)**, or **nosocomial infections**, are acquired in a clinical setting. Transmission is facilitated by medical interventions and the high concentration of susceptible, immunocompromised individuals in clinical settings.

## Footnotes


1. Yves Thomas, Guido Vogel, Werner Wunderli, Patricia Suter, Mark Witschi, Daniel Koch, Caroline Tapparel, and Laurent Kaiser. "Survival of Influenza Virus on Banknotes." *Applied and Environmental Microbiology* 74, no. 10 (2008): 3002–3007.
2. Filio Marineli, Gregory Tsoucalas, Marianna Karamanou, and George Androutsos. "Mary Mallon (1869–1938) and the History of Typhoid Fever." *Annals of Gastroenterology* 26 (2013): 132–134. www.ncbi.nlm.nih.gov/pmc/arti...rol-26-132.pdf.
3. World Health Organization. Fact sheet No. 391—*Drinking Water*. June 2005. www.who.int/mediacentre/factsheets/fs391/en.
4. Blandine Massonnet-Bruneel, Nicole Corre-Catelin, Renaud Lacroix, Rosemary S. Lees, Kim Phuc Hoang, Derric Nimmo, Luke Alphey, and Paul Reiter. "Fitness of Transgenic Mosquito *Aedes aegypti* Males Carrying a Dominant Lethal Genetic System." *PLOS ONE* 8, no. 5 (2013): e62711.
5. Richard Levine. "Cases of Dengue Drop 91 Percent Due to Genetically Modified Mosquitoes." *Entomology Today*. entomologytoday.org/2016/07/...ied-mosquitoes.
6. Olivia Judson. "A Bug's Death." *The New York Times*, September 25, 2003. www.nytimes.com/2003/09/25/op...g-s-death.html.
7. Gilda Grard, Mélanie Caron, Illich Manfred Mombo, Dieudonné Nkoghe, Statiana Mboui Ondo, Davy Jiolle, Didier Fontenille, Christophe Paupy, and Eric Maurice Leroy. "Zika Virus in Gabon (Central Africa)–2007: A New Threat from *Aedes albopictus*?" *PLOS Neglected Tropical Diseases* 8, no. 2 (2014): e2681.
8. Constância F.J. Ayres. "Identification of Zika Virus Vectors and Implications for Control." *The Lancet Infectious Diseases* 16, no. 3 (2016): 278–279.
9. Centers for Disease Control and Prevention. "HAI Data and Statistics." 2016. http://www.cdc.gov/hai/surveillance. Accessed Jan 2, 2016.



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# 14.3: Global Public Health

**Learning Objectives**

- Describe the entities involved in international public health and their activities
- Identify and differentiate between emerging and reemerging infectious diseases

A large number of international programs and agencies are involved in efforts to promote global public health. Among their goals are developing infrastructure in health care, public sanitation, and public health capacity; monitoring infectious disease occurrences around the world; coordinating communications between national public health agencies in various countries; and coordinating international responses to major health crises. In large part, these international efforts are necessary because disease-causing microorganisms know no national boundaries.

## The World Health Organization (WHO)

International public health issues are coordinated by the World Health Organization (WHO), an agency of the United Nations. Of its roughly $4 billion budget for 2015–16[1], about $1 billion was funded by member states and the remaining $3 billion by voluntary contributions. In addition to monitoring and reporting on infectious disease, WHO also develops and implements strategies for their control and prevention. WHO has had a number of successful international public health campaigns. For example, its vaccination program against smallpox, begun in the mid-1960s, resulted in the global eradication of the disease by 1980. WHO continues to be involved in infectious disease control, primarily in the developing world, with programs targeting malaria, HIV/AIDS, and tuberculosis, among others. It also runs programs to reduce illness and mortality that occur as a result of violence, accidents, lifestyle-associated illnesses such as diabetes, and poor health-care infrastructure.

WHO maintains a global alert and response system that coordinates information from member nations. In the event of a public health emergency or epidemic, it provides logistical support and coordinates international response to the emergency. The United States contributes to this effort through the CDC. The CDC carries out international monitoring and public health efforts, mainly in the service of protecting US public health in an increasingly connected world. Similarly, the European Union maintains a Health Security Committee that monitors disease outbreaks within its member countries and internationally, coordinating with WHO.

**Exercise 14.3.1**

Name the organizations that participate in international public health monitoring.

## Emerging and Reemerging Infectious Diseases

Both WHO and some national public health agencies such as the CDC monitor and prepare for emerging infectious diseases. An emerging infectious disease is either new to the human population or has shown an increase in prevalence in the previous twenty years. Whether the disease is new or conditions have changed to cause an increase in frequency, its status as emerging implies the need to apply resources to understand and control its growing impact.

Emerging diseases may change their frequency gradually over time, or they may experience sudden epidemic growth. The importance of vigilance was made clear during the Ebola hemorrhagic fever epidemic in western Africa through 2014–2015. Although health experts had been aware of the Ebola virus since the 1970s, an outbreak on such a large scale had never happened before (Figure 14.3.1). Previous human epidemics had been small, isolated, and contained. Indeed, the gorilla and chimpanzee populations of western Africa had suffered far worse from Ebola than the human population. The pattern of small isolated human epidemics changed in 2014. Its high transmission rate, coupled with cultural practices for treatment of the dead and perhaps its emergence in an urban setting, caused the disease to spread rapidly, and thousands of people died. The international public health community responded with a large emergency effort to treat patients and contain the epidemic.

Emerging diseases are found in all countries, both developed and developing (Table 14.3.1). Some nations are better equipped

to deal with them. National and international public health agencies watch for epidemics like the Ebola outbreak in developing countries because those countries rarely have the health-care infrastructure and expertise to deal with large outbreaks effectively. Even with the support of international agencies, the systems in western Africa struggled to identify and care for the sick and control spread. In addition to the altruistic goal of saving lives and assisting nations lacking in resources, the global nature of transportation means that an outbreak anywhere can spread quickly to every corner of the planet. Managing an epidemic in one location—its source—is far easier than fighting it on many fronts.

Ebola is not the only disease that needs to be monitored in the global environment. In 2015, WHO set priorities on several emerging diseases that had a high probability of causing epidemics and that were poorly understood (and thus urgently required research and development efforts).

A reemerging infectious disease is a disease that is increasing in frequency after a previous period of decline. Its reemergence may be a result of changing conditions or old prevention regimes that are no longer working. Examples of such diseases are drug-resistant forms of tuberculosis, bacterial pneumonia, and malaria. Drug-resistant strains of the bacteria causing gonorrhea and syphilis are also becoming more widespread, raising concerns of untreatable infections.

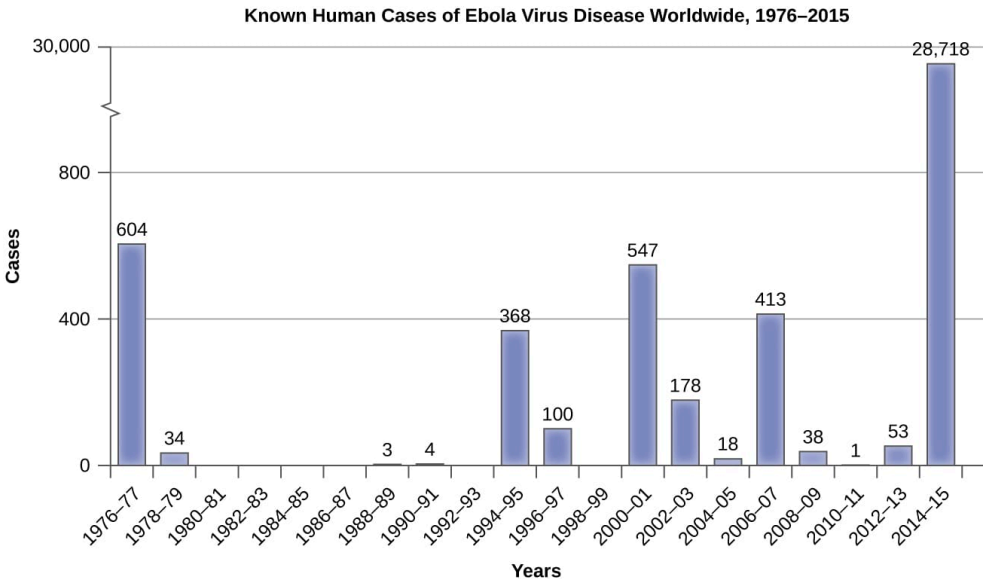



Figure 14.3.1: Even before the Ebola epidemic of 2014–15, Ebola was considered an emerging disease because of several smaller outbreaks between the mid-1990s and 2000s.

*Table 14.3.1: Some Emerging and Reemerging Infectious Diseases*

| Disease | Pathogen | Year Discovered | Affected Regions | Transmission |
|---|---|---|---|---|
| AIDS | HIV | 1981 | Worldwide | Contact with infected body fluids |
| Chikungunya fever | Chikungunya virus | 1952 | Africa, Asia, India; spreading to Europe and the Americas | Mosquito-borne |
| Ebola virus disease | Ebola virus | 1976 | Central and Western Africa | Contact with infected body fluids |
| H1N1 Influenza (swine flu) | H1N1 virus | 2009 | Worldwide | Droplet transmission |
| Lyme disease | *Borrelia burgdorferi* bacterium | 1981 | Northern hemisphere | From mammal reservoirs to humans by tick vectors |
| West Nile virus disease | West Nile virus | 1937 | Africa, Australia, Canada to Venezuela, Europe, Middle East, Western Asia | Mosquito-borne |

## Exercise 14.3.2

1. Explain why it is important to monitor emerging infectious diseases.
2. Explain how a bacterial disease could reemerge, even if it had previously been successfully treated and controlled.

## Micro Connections

**SARS Outbreak and Identification**

On November 16, 2002, the first case of a SARS outbreak was reported in Guangdong Province, China. The patient exhibited influenza-like symptoms such as fever, cough, myalgia, sore throat, and shortness of breath. As the number of cases grew, the Chinese government was reluctant to openly communicate information about the epidemic with the World Health Organization (WHO) and the international community. The slow reaction of Chinese public health officials to this new disease contributed to the spread of the epidemic within and later outside China. In April 2003, the Chinese government finally responded with a huge public health effort involving quarantines, medical checkpoints, and massive cleaning projects. Over 18,000 people were quarantined in Beijing alone. Large funding initiatives were created to improve health-care facilities, and dedicated outbreak teams were created to coordinate the response. By August 16, 2003, the last SARS patients were released from a hospital in Beijing nine months after the first case was reported in China.

In the meantime, SARS spread to other countries on its way to becoming a global pandemic. Though the infectious agent had yet to be identified, it was thought to be an influenza virus. The disease was named SARS, an acronym for severe acute respiratory syndrome, until the etiologic agent could be identified. Travel restrictions to Southeast Asia were enforced by many countries. By the end of the outbreak, there were 8,098 cases and 774 deaths worldwide. China and Hong Kong were hit hardest by the epidemic, but Taiwan, Singapore, and Toronto, Canada, also saw significant numbers of cases (Figure 14.3.2 ).

Fortunately, timely public health responses in many countries effectively suppressed the outbreak and led to its eventual containment. For example, the disease was introduced to Canada in February 2003 by an infected traveler from Hong Kong, who died shortly after being hospitalized. By the end of March, hospital isolation and home quarantine procedures were in place in the Toronto area, stringent anti-infection protocols were introduced in hospitals, and the media were actively reporting on the disease. Public health officials tracked down contacts of infected individuals and quarantined them. A total of 25,000 individuals were quarantined in the city. Thanks to the vigorous response of the Canadian public health community, SARS was brought under control in Toronto by June, a mere four months after it was introduced.

In 2003, WHO established a collaborative effort to identify the causative agent of SARS, which has now been identified as a coronavirus that was associated with horseshoe bats. The genome of the SARS virus was sequenced and published by researchers at the CDC and in Canada in May 2003, and in the same month researchers in the Netherlands confirmed the etiology of the disease by fulfilling Koch's postulates for the SARS coronavirus. The last known case of SARS worldwide was reported in 2004.

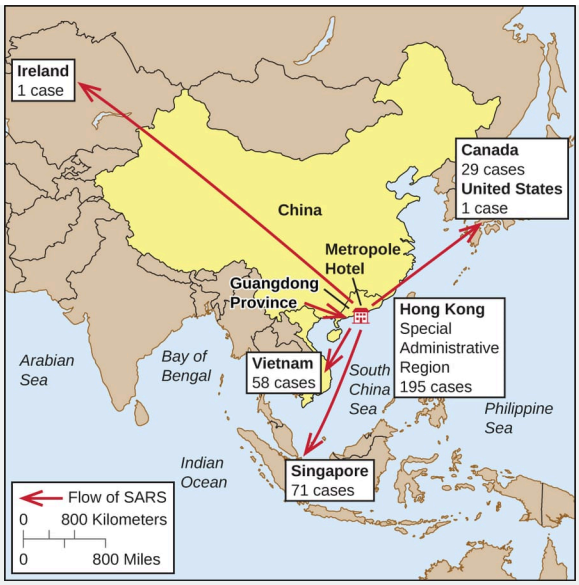



Figure 14.3.2: This map shows the spread of SARS as of March 28, 2003. (credit: modification of work by Central Intelligence Agency)

**Link to Learning**

This database of reports chronicles outbreaks of infectious disease around the world. It was on this system that the first information about the SARS outbreak in China emerged.

The CDC publishes *Emerging Infectious Diseases*, a monthly journal available online.

## Key Concepts and Summary

- The **World Health Organization (WHO)** is an agency of the United Nations that collects and analyzes data on disease occurrence from member nations. WHO also coordinates public health programs and responses to international health emergencies.
- **Emerging diseases** are those that are new to human populations or that have been increasing in the past two decades. **Reemerging diseases** are those that are making a resurgence in susceptible populations after previously having been controlled in some geographic areas.

## Footnotes

1. World Health Organization. “Programme Budget 2014–2015.” www.who.int/about/finances-accountability/budget/en.

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# 14.4: Review Questions

## Multiple Choice

1. Which is the most common type of biological vector of human disease?
   A. viruses
   B. bacteria
   C. mammals
   D. arthropods

*Answer available at the end of this section.*

2. A mosquito bites a person who subsequently develops a fever and abdominal rash. What type of transmission would this be?
   A. mechanical vector transmission
   B. biological vector transmission
   C. direct contact transmission
   D. vehicle transmission

*Answer available at the end of this section.*

3. Cattle are allowed to pasture in a field that contains the farmhouse well, and the farmer's family becomes ill with a gastrointestinal pathogen after drinking the water. What type of transmission of infectious agents would this be?
   A. biological vector transmission
   B. direct contact transmission
   C. indirect contact transmission
   D. vehicle transmission

*Answer available at the end of this section.*

4. A blanket from a child with chickenpox is likely to be contaminated with the virus that causes chickenpox (Varicella-zoster virus). What is the blanket called?
   A. fomite
   B. host
   C. pathogen
   D. vector

*Answer available at the end of this section.*

5. Which of the following would NOT be considered an emerging disease?
   A. Ebola hemorrhagic fever
   B. West Nile virus fever/encephalitis
   C. Zika virus disease
   D. Tuberculosis

*Answer available at the end of this section.*

6. Which of the following would NOT be considered a reemerging disease?
   A. Drug-resistant tuberculosis
   B. Drug-resistant gonorrhea
   C. Malaria
   D. West Nile virus fever/encephalitis

*Answer available at the end of this section.*

7. Which of the following factors can lead to reemergence of a disease?
   A. A mutation that allows it to infect humans
   B. A period of decline in vaccination rates
   C. A change in disease reporting procedures
   D. Better education on the signs and symptoms of the disease

*Answer available at the end of this section.*

8. Why are emerging diseases with very few cases the focus of intense scrutiny?
   A. They tend to be more deadly
   B. They are increasing and therefore not controlled
   C. They naturally have higher transmission rates
   D. They occur more in developed countries

*Answer available at the end of this section.*

## Matching

9. Match each term with its description.

| | |
|---|---|
| ___sporadic disease | A. the number of disease cases per 100,000 individuals |
| ___endemic disease | B. a disease in higher than expected numbers around the world |
| ___pandemic disease | C. the number of deaths from a disease for every 10,000 individuals |
| ___morbidity rate | D. a disease found occasionally in a region with cases occurring mainly in isolation from each other |
| ___mortality rate | E. a disease found regularly in a region |

*Answer available at the end of this section.*

## Fill in the Blank

10. The _____ collects data and conducts epidemiologic studies in the United States.

*Answer available at the end of this section.*

11. A patient in the hospital with a urinary catheter develops a bladder infection. This is an example of a(n) _____ infection.

*Answer available at the end of this section.*

12. A _____ is an animal that can transfer infectious pathogens from one host to another.

*Answer available at the end of this section.*

13. The _____ collects data and conducts epidemiologic studies at the global level.

*Answer available at the end of this section.*

## Short Answer

14. During an epidemic, why might the prevalence of a disease at a particular time not be equal to the sum of the incidences of the disease?
15. In what publication would you find data on emerging/reemerging diseases in the United States?
16. Differentiate between droplet vehicle transmission and airborne transmission.

## Critical Thinking

17. Why might an epidemiological population in a state not be the same size as the number of people in a state? Use an example.
18. Many people find that they become ill with a cold after traveling by airplane. The air circulation systems of commercial aircraft use HEPA filters that should remove any infectious agents that pass through them. What are the possible reasons for increased incidence of colds after flights?
19. An Atlantic crossing by boat from England to New England took 60–80 days in the 18th century. In the late 19th century the voyage took less than a week. How do you think these time differences for travel might have impacted the spread of infectious diseases from Europe to the Americas, or vice versa?

## Answers

**Multiple Choice**
D

**Multiple Choice**
B

**Multiple Choice**
D

**Multiple Choice**
A

**Multiple Choice**
D

**Multiple Choice**
D

**Multiple Choice**
B

**Multiple Choice**
B

**Matching**
D, E, B, A, C

**Fill in the Blank**
Centers for Disease Control and Prevention, or CDC

**Fill in the Blank**
nosocomial or healthcare-associated

**Fill in the Blank**
vector

**Fill in the Blank**
WHO (World Health Organization)

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# 14: DISEASE AND EPIDEMIOLOGY (PART B)

Epidemiology studies how disease originates and spreads throughout a population, with the goal of preventing outbreaks and containing them when they do occur. Over the past two centuries, discoveries in epidemiology have led to public health policies that have transformed life in developed nations, leading to the eradication (or near eradication) of many diseases that were once causes of great human suffering and premature death. However, the work of epidemiologists is far from finished. Numerous diseases continue to plague humanity, and new diseases are always emerging. Moreover, in the developing world, lack of infrastructure continues to pose many challenges to efforts to contain disease.

## Chapter Outline


14.1: The Language of Epidemiologists

14.2: How Diseases Spread

14.3: Global Public Health

14.4: Review Questions



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# WEEK 10

## 15: Circulatory and Lymphatic System Infections (Part A)

15.1: Arthropod-Borne Viral Diseases

15.2: Parasitic Infections of the Circulatory and Lymphatic Systems

15.3: Review Questions

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# 15.1: Arthropod-Borne Viral Diseases

There are a number of arthropod-borne viruses, or arboviruses, that can cause human disease. Among these are several important hemorrhagic fevers transmitted by mosquitoes. We will discuss three that pose serious threats: yellow fever, chikungunya fever, and dengue fever.

## Yellow Fever

Yellow fever was once common in the US and caused several serious outbreaks between 1700 and 1900.[1] Through vector control efforts, however, this disease has been eliminated in the US. Currently, yellow fever occurs primarily in tropical and subtropical areas in South America and Africa. It is caused by the yellow fever virus of the genus *Flavivirus* (named for the Latin word *flavus* meaning *yellow*), which is transmitted to humans by mosquito vectors. Sylvatic yellow fever occurs in tropical jungle regions of Africa and Central and South America, where the virus can be transmitted from infected monkeys to humans by the mosquitoes *Aedes africanus* or *Haemagogus* spp. In urban areas, the *Aedes aegypti* mosquito is mostly responsible for transmitting the virus between humans.

Most individuals infected with yellow fever virus have no illness or only mild disease. Onset of milder symptoms is sudden, with dizziness, fever of 39–40 °C (102–104 °F), chills, headache, and myalgias. As symptoms worsen, the face becomes flushed, and nausea, vomiting, constipation, severe fatigue, restlessness, and irritability are common. Mild disease may resolve after 1 to 3 days. However, approximately 15% of cases progress to develop moderate to severe yellow fever disease.[2]

In moderate or severe disease, the fever falls suddenly 2 to 5 days after onset, but recurs several hours or days later. Symptoms of jaundice, petechial rash, mucosal hemorrhages, oliguria (scant urine), epigastric tenderness with bloody vomit, confusion, and apathy also often occur for approximately 7 days of moderate to severe disease. After more than a week, patients may have a rapid recovery and no sequelae.

In its most severe form, called malignant yellow fever, symptoms include delirium, bleeding, seizures, shock, coma, and multiple organ failure; in some cases, death occurs. Patients with malignant yellow fever also become severely immunocompromised, and even those in recovery may become susceptible to bacterial superinfections and pneumonia. Of the 15% of patients who develop moderate or severe disease, up to half may die.

Diagnosis of yellow fever is often based on clinical signs and symptoms and, if applicable, the patient's travel history, but infection can be confirmed by culture, serologic tests, and PCR. There are no effective treatments for patients with yellow fever. Whenever possible, patients with yellow fever should be hospitalized for close observation and given supportive care. Prevention is the best method of controlling yellow fever. Use of mosquito netting, window screens, insect repellents, and insecticides are all effective methods of reducing exposure to mosquito vectors. An effective vaccine is also available, but in the US, it is only administered to those traveling to areas with endemic yellow fever. In West Africa, the World Health Organization (WHO) launched a Yellow Fever Initiative in 2006 and, since that time, significant progress has been made in combating yellow fever. More than 105 million people have been vaccinated, and no outbreaks of yellow fever were reported in West Africa in 2015.

### Micro Connections

**Yellow Fever: Altering the Course of History**

Yellow fever originated in Africa and is still most prevalent there today. This disease is thought to have been translocated to the Americas by the slave trade in the 16th century.[3] Since that time, yellow fever has been associated with many severe outbreaks, some of which had important impacts upon historic events.

Yellow fever virus was once an important cause of disease in the US. In the summer of 1793, there was a serious outbreak in Philadelphia (then the US capitol). It is estimated that 5,000 people (10% of the city's population) died. All of the government officials, including George Washington, fled the city in the face of this epidemic. The disease only abated when autumn frosts killed the mosquito vector population.

In 1802, Napoleon Bonaparte sent an army of 40,000 to Hispaniola to suppress a slave revolution. This was seen by many as a part of a plan to use the Louisiana Territory as a granary as he reestablished France as a global power. Yellow fever, however, decimated his army and they were forced to withdraw. Abandoning his aspirations in the New World, Napoleon sold the Louisiana Territory to the US for $15 million in 1803.

The most famous historic event associated with yellow fever is probably the construction of the Panama Canal. The French began work on the canal in the early 1880s. However, engineering problems, malaria, and yellow fever forced them to abandon the project. The US took over the task in 1904 and opened the canal a decade later. During those 10 years, yellow fever was a constant adversary. In the first few years of work, greater than 80% of the American workers in Panama were hospitalized with yellow fever. It was the work of Carlos Finlay and Walter Reed that turned the tide. Taken together, their work demonstrated that the disease was transmitted by mosquitoes. Vector control measures succeeded in reducing both yellow fever and malaria rates and contributed to the ultimate success of the project.

## Dengue Fever

The disease dengue fever, also known as breakbone fever, is caused by four serotypes of dengue virus called dengue 1–4. These are *Flavivirus* species that are transmitted to humans by *A. aegypti* or *A. albopictus* mosquitoes. The disease is distributed worldwide but is predominantly located in tropical regions. The WHO estimates that 50 million to 100 million infections occur yearly, including 500,000 dengue hemorrhagic fever (DHF) cases and 22,000 deaths, most among children.[4] Dengue fever is primarily a self-limiting disease characterized by abrupt onset of high fever up to 40 °C (104 °F), intense headaches, rash, slight nose or gum bleeding, and extreme muscle, joint, and bone pain, causing patients to feel as if their bones are breaking, which is the reason this disease is also referred to as breakbone fever. As the body temperature returns to normal, in some patients, signs of dengue hemorrhagic fever may develop that include drowsiness, irritability, severe abdominal pain, severe nose or gum bleeding, persistent vomiting, vomiting blood, and black tarry stools, as the disease progresses to DHF or dengue shock syndrome (DSS). Patients who develop DHF experience circulatory system failure caused by increased blood vessel permeability. Patients with dengue fever can also develop DSS from vascular collapse because of the severe drop in blood pressure. Patients who develop DHF or DSS are at greater risk for death without prompt appropriate supportive treatment. About 30% of patients with severe hemorrhagic disease with poor supportive treatment die, but mortality can be less than 1% with experienced support.[5]

Diagnostic tests for dengue fever include serologic testing, ELISA, and reverse transcriptase-polymerase chain reaction (RT-PCR) of blood. There are no specific treatments for dengue fever, nor is there a vaccine. Instead, supportive clinical care is provided to treat the symptoms of the disease. The best way to limit the impact of this viral pathogen is vector control.

## Chikungunya Fever

The arboviral disease chikungunya fever is caused by chikungunya virus (CHIKV), which is transmitted to humans by *A. aegypti* and *A. albopictus* mosquitoes. Until 2013, the disease had not been reported outside of Africa, Asia, and a few European countries; however, CHIKV has now spread to mosquito populations in North and South America. Chikungunya fever is characterized by high fever, joint pain, rash, and blisters, with joint pain persisting for several months. These infections are typically self-limiting and rarely fatal.

The diagnostic approach for chikungunya fever is similar to that for dengue fever. Viruses can be cultured directly from patient serum during early infections. IFA, EIA, ELISA, PCR, and RT-PCR are available to detect CHIKV antigens and patient antibody response to the infection. There are no specific treatments for this disease except to manage symptoms with fluids, analgesics, and bed rest. As with most arboviruses, the best strategy for combating the disease is vector control.

### Link to Learning

Use this interactive map to explore the global distribution of dengue.

### Exercise 15.1.2

1. Name three arboviral diseases and explain why they are so named.

2. What is the best method for controlling outbreaks of arboviral diseases?

*Answer available at the end of this section.*

## Key Concepts and Summary

- Arboviral diseases such as **yellow fever, dengue fever,** and **chikungunya fever** are characterized by high fevers and vascular damage that can often be fatal.
- Although there is a vaccine available for yellow fever, treatments for patients with yellow fever, dengue, and chikungunya fever are limited to supportive therapies.
- Vector control and animal reservoir control remain the best defenses against most viruses that cause diseases of the circulatory system.

## Footnotes


1. Centers for Disease Control and Prevention. "History Timeline Transcript." http://www.cdc.gov/travel-training/local/HistoryEpidemiologyandVaccination/HistoryTimelineTranscript.pdf. Accessed July 28, 2016.
2. Centers for Disease Control and Prevention. "Yellow Fever, Symptoms and Treatment." 2015 http://www.cdc.gov/yellowfever/symptoms/index.html. Accessed July 28, 2016.
3. J.T. Cathey, J.S. Marr. "Yellow fever, Asia and the East African Slave Trade." *Transactions of the Royal Society of Tropical Medicine and Hygiene* 108, no. 5 (2014):252–257.
4. Centers for Disease Control and Prevention. "Dengue, Epidemiology." 2014. http://www.cdc.gov/dengue/epidemiology/index.html. Accessed July 28, 2016.
5. C.R. Pringle "Dengue." MSD Manual: Consumer Version. https://www.msdmanuals.com/home/infections/viral-infections/dengue. 2016. Accessed Sept 15, 2016.


### Answers

**Exercise** 15.1.2


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# 15.2: Parasitic Infections of the Circulatory and Lymphatic Systems

**Learning Objectives**

- Identify common parasites that cause infections of the circulatory and lymphatic systems
- Compare the major characteristics of specific parasitic diseases affecting the circulatory and lymphatic systems

Some protozoa and parasitic flukes are also capable of causing infections of the human circulatory system. Although these infections are rare in the US, they continue to cause widespread suffering in the developing world today. Fungal infections of the circulatory system are very rare. Therefore, they are not discussed in this chapter.

## Malaria

Despite more than a century of intense research and clinical advancements, malaria remains one of the most important infectious diseases in the world today. Its widespread distribution places more than half of the world's population in jeopardy. In 2015, the WHO estimated there were about 214 million cases of malaria worldwide, resulting in about 438,000 deaths; about 88% of cases and 91% of deaths occurred in Africa.[1] Although malaria is not currently a major threat in the US, the possibility of its reintroduction is a concern. Malaria is caused by several protozoan parasites in the genus *Plasmodium*: *P. falciparum, P. knowlesi, P. malariae, P. ovale,* and *P. vivax*. *Plasmodium* primarily infect red blood cells and are transmitted through the bite of *Anopheles* mosquitoes.

Currently, *P. falciparum* is the most common and most lethal cause of malaria, often called falciparum malaria. Falciparum malaria is widespread in highly populated regions of Africa and Asia, putting many people at risk for the most severe form of the disease.

The classic signs and symptoms of malaria are cycles of extreme fever and chills. The sudden, violent symptoms of malaria start with malaise, abrupt chills, and fever (39–41° C [102.2–105.8 °F]), rapid and faint pulse, polyuria, headache, myalgia, nausea, and vomiting. After 2 to 6 hours of these symptoms, the fever falls, and profuse sweating occurs for 2 to 3 hours, followed by extreme fatigue. These symptoms are a result of *Plasmodium* emerging from red blood cells synchronously, leading to simultaneous rupture of a large number of red blood cells, resulting in damage to the spleen, liver, lymph nodes, and bone marrow. The organ damage resulting from hemolysis causes patients to develop sludge blood (i.e., blood in which the red blood cells agglutinate into clumps) that can lead to lack of oxygen, necrosis of blood vessels, organ failure, and death.

In established infections, malarial cycles of fever and chills typically occur every 2 days in the disease described as tertian malaria, which is caused by *P. vivax* and *P. ovale*. The cycles occur every 3 days in the disease described as quartan malaria, which is caused by *P. malariae*. These intervals may vary among cases.

*Plasmodium* has a complex life cycle that includes several developmental stages alternately produced in mosquitoes and humans (Figure 15.2.1). When an infected mosquito takes a blood meal, sporozoites in the mosquito salivary gland are injected into the host's blood. These parasites circulate to the liver, where they develop into schizonts. The schizonts then undergo schizogony, resulting in the release of many merozoites at once. The merozoites move to the bloodstream and infect red blood cells. Inside red blood cells, merozoites develop into trophozoites that produce more merozoites. The synchronous release of merozoites from red blood cells in the evening leads to the symptoms of malaria.

In addition, some trophozoites alternatively develop into male and female gametocytes. The gametocytes are taken up when the mosquito takes a blood meal from an infected individual. Sexual sporogony occurs in the gut of the mosquito. The gametocytes fuse to form zygotes in the insect gut. The zygotes become motile and elongate into an ookinete. This form penetrates the midgut wall and develops into an oocyst. Finally, the oocyst releases new sporozoites that migrate to the mosquito salivary glands to complete the life cycle.

Diagnosis of malaria is by microscopic observation of developmental forms of *Plasmodium* in blood smears and rapid EIA assays that detect *Plasmodium* antigens or enzymes (Figure 15.2.2). Drugs such as chloroquine, atovaquone , artemether, and lumefantrine may be prescribed for both acute and prophylactic therapy, although some *Plasmodium* spp. have shown resistance

to antimalarial drugs. Use of insecticides and insecticide-treated bed nets can limit the spread of malaria. Despite efforts to develop a vaccine for malaria, none is currently available.

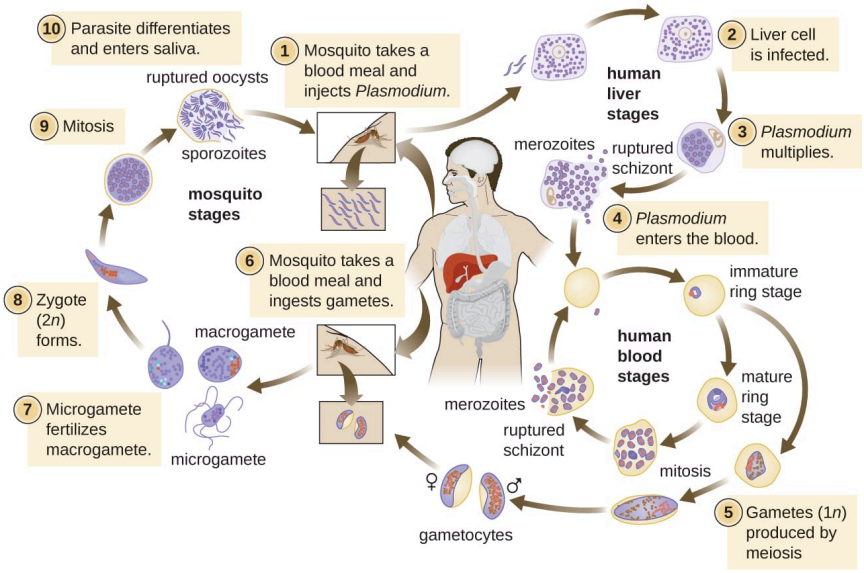



Figure 15.2.1: The life cycle of *Plasmodium*. (credit: modification of work by Centers for Disease Control and Prevention)

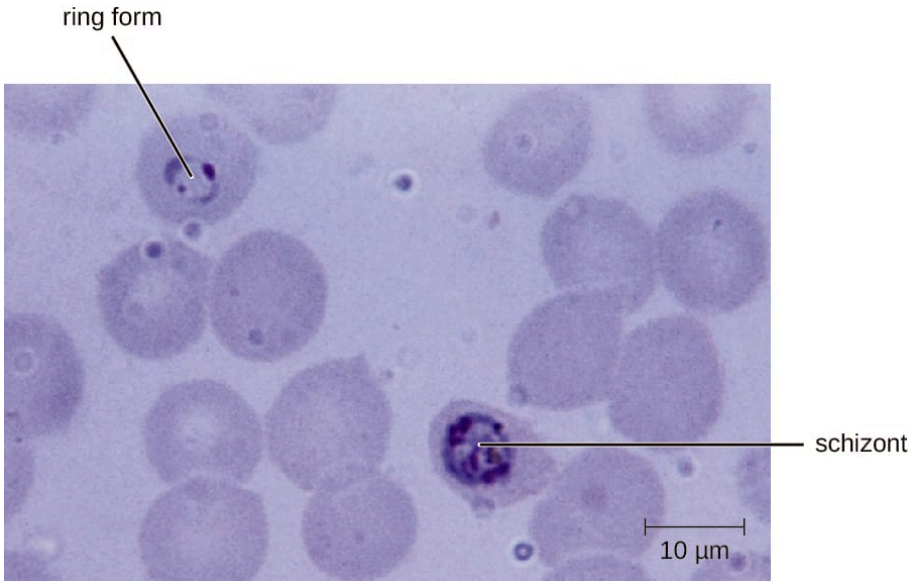



Figure 15.2.2: A blood smear (human blood stage) shows an early trophozoite in a delicate ring form (upper left) and an early stage schizont form (center) of *Plasmodium falciparum* from a patient with malaria. (credit: modification of work by Centers for Disease Control and Prevention)

## Link to Learning

The Nothing But Nets campaign, an initiative of the United Nations Foundation, has partnered with the Bill and Melinda Gates Foundation to make mosquito bed nets available in developing countries in Africa. Visit their website to learn more about their efforts to prevent malaria.

## Exercise 15.2.1

Why is malaria one of the most important infectious diseases?

# Toxoplasmosis

The disease toxoplasmosis is caused by the protozoan *Toxoplasma gondii*. *T. gondii* is found in a wide variety of birds and mammals,[2] and human infections are common. The Centers for Disease Control and Prevention (CDC) estimates that 22.5% of the population 12 years and older has been infected with *T. gondii*; but immunocompetent individuals are typically asymptomatic, however.[3] Domestic cats are the only known definitive hosts for the sexual stages of *T. gondii* and, thus, are the main reservoirs of infection. Infected cats shed *T. gondii* oocysts in their feces, and these oocysts typically spread to humans through contact with fecal matter on cats' bodies, in litter boxes, or in garden beds where outdoor cats defecate.

*T. gondii* has a complex life cycle that involves multiple hosts. The *T. gondii* life cycle begins when unsporulated oocysts are shed in the cat's feces. These oocysts take 1–5 days to sporulate in the environment and become infective. Intermediate hosts in nature include birds and rodents, which become infected after ingesting soil, water, or plant material contaminated with the infective oocysts. Once ingested, the oocysts transform into tachyzoites that localize in the bird or rodent neural and muscle tissue, where they develop into tissue cysts. Cats may become infected after consuming birds and rodents harboring tissue cysts. Cats and other animals may also become infected directly by ingestion of sporulated oocysts in the environment. Interestingly, *Toxoplasma* infection appears to be able to modify the host's behavior. Mice infected by *Toxoplasma* lose their fear of cat pheromones. As a result, they become easier prey for cats, facilitating the transmission of the parasite to the cat definitive host[4] (Figure 15.2.3).

*Toxoplasma* infections in humans are extremely common, but most infected people are asymptomatic or have subclinical symptoms. Some studies suggest that the parasite may be able to influence the personality and psychomotor performance of infected humans, similar to the way it modifies behavior in other mammals.[5] When symptoms do occur, they tend to be mild and similar to those of mononucleosis. However, asymptomatic toxoplasmosis can become problematic in certain situations. Cysts can lodge in a variety of human tissues and lie dormant for years. Reactivation of these quiescent infections can occur in immunocompromised patients following transplantation, cancer therapy, or the development of an immune disorder such as AIDS. In patients with AIDS who have toxoplasmosis, the immune system cannot combat the growth of *T. gondii* in body tissues; as a result, these cysts can cause encephalitis, retinitis, pneumonitis, cognitive disorders, and seizures that can eventually be fatal.

Toxoplasmosis can also pose a risk during pregnancy because tachyzoites can cross the placenta and cause serious infections in the developing fetus. The extent of fetal damage resulting from toxoplasmosis depends on the severity of maternal disease, the damage to the placenta, the gestational age of the fetus when infected, and the virulence of the organism. Congenital toxoplasmosis often leads to fetal loss or premature birth and can result in damage to the central nervous system, manifesting as mental retardation, deafness, or blindness. Consequently, pregnant women are advised by the CDC to take particular care in preparing meat, gardening, and caring for pet cats.[6] Diagnosis of toxoplasmosis infection during pregnancy is usually achieved by serology including TORCH testing (the "T" in TORCH stands for toxoplasmosis). Diagnosis of congenital infections can also be achieved by detecting *T. gondii* DNA in amniotic fluid, using molecular methods such as PCR.

In adults, diagnosis of toxoplasmosis can include observation of tissue cysts in tissue specimens. Tissue cysts may be observed in Giemsa- or Wright-stained biopsy specimens, and CT, magnetic resonance imaging, and lumbar puncture can also be used to confirm infection (Figure 15.2.4).

Preventing infection is the best first-line defense against toxoplasmosis. Preventive measures include washing hands thoroughly after handling raw meat, soil, or cat litter, and avoiding consumption of vegetables possibly contaminated with cat feces. All meat should be cooked to an internal temperature of 73.9–76.7 °C (165–170 °F).

Most immunocompetent patients do not require clinical intervention for *Toxoplasma* infections. However, neonates, pregnant women, and immunocompromised patients can be treated with pyrimethamine and sulfadiazine—except during the first trimester of pregnancy, because these drugs can cause birth defects. Spiramycin has been used safely to reduce transmission in pregnant women with primary infection during the first trimester because it does not cross the placenta.

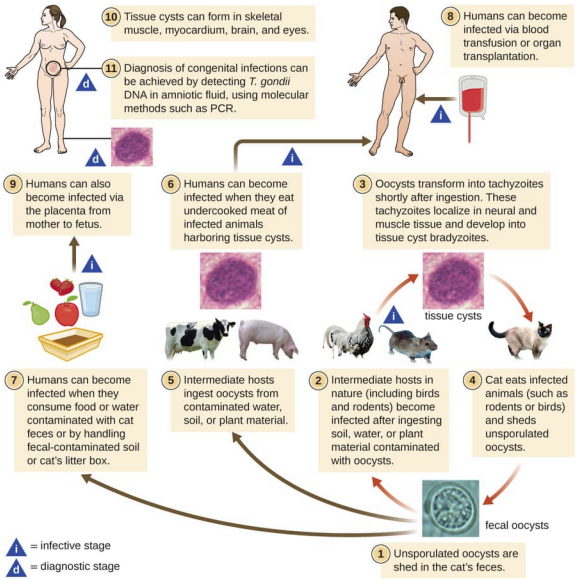



Figure 15.2.3: The infectious cycle of *Toxoplasma gondii*. (credit: "diagram": modification of work by Centers for Disease Control and Prevention; credit "cat": modification of work by "KaCey97078"/Flickr)

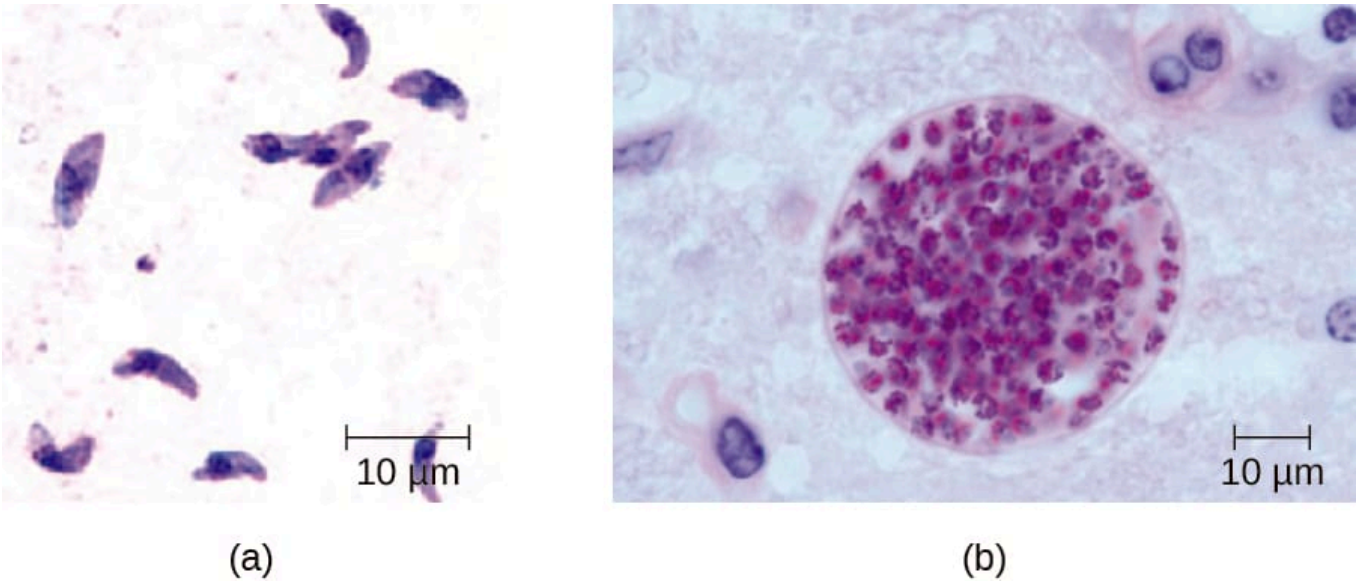



Figure 15.2.4: (a) Giemsa-stained *Toxoplasma gondii* tachyzoites from a smear of peritoneal fluid obtained from a mouse inoculated with *T. gondii*. Tachyzoites are typically crescent shaped with a prominent, centrally placed nucleus. (b) Microscopic cyst containing *T. gondii* from mouse brain tissue. Thousands of resting parasites (stained red) are contained in a thin parasite cyst wall. (credit a: modification of work by Centers for Disease Control and Prevention; credit b: modification of work by USDA)

**Exercise 15.2.2**

How does *T. gondii* infect humans?

## Babesiosis

Babesiosis is a rare zoonotic infectious disease caused by *Babesia* spp. These parasitic protozoans infect various wild and domestic animals and can be transmitted to humans by black-legged *Ixodes* ticks. In humans, *Babesia* infect red blood cells and replicate inside the cell until it ruptures. The *Babesia* released from the ruptured red blood cell continue the growth cycle by invading other red blood cells. Patients may be asymptomatic, but those who do have symptoms often initially experience malaise, fatigue, chills, fever, headache, myalgia, and arthralgia. In rare cases, particularly in asplenic (absence of the spleen)

patients, the elderly, and patients with AIDS, babesiosis may resemble falciparum malaria, with high fever, hemolytic anemia, hemoglobinuria (hemoglobin or blood in urine), jaundice, and renal failure, and the infection can be fatal. Previously acquired asymptomatic Babesia infection may become symptomatic if a splenectomy is performed.

Diagnosis is based mainly on the microscopic observation of parasites in blood smears (Figure 15.2.5). Serologic and antibody detection by IFA can also be performed and PCR-based tests are available. Many people do not require clinical intervention for Babesia infections, however, serious infections can be cleared with a combination of atovaquone and azithromycin or a combination of clindamycin and quinine.

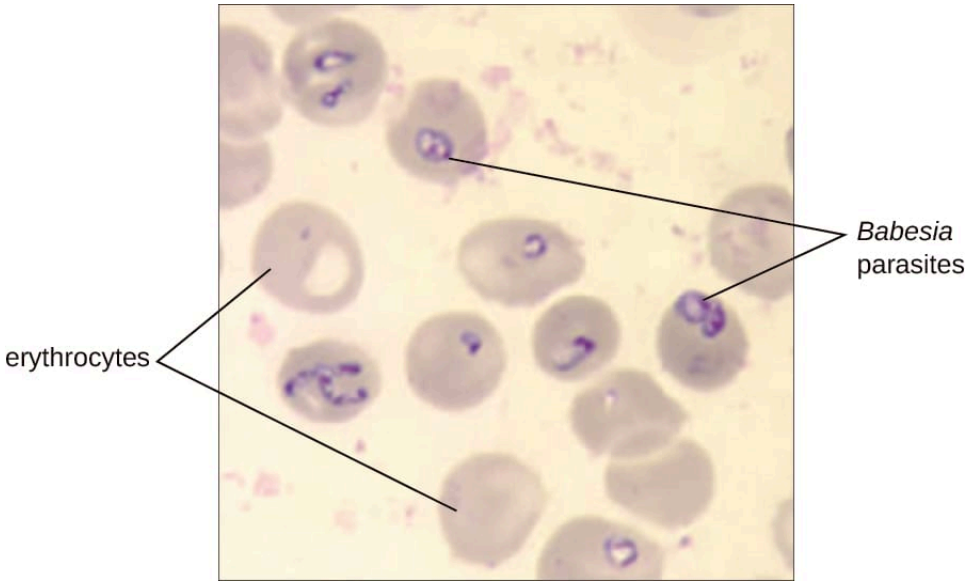



Figure 15.2.5: In this blood smear from a patient with babesiosis, *Babesia* parasites can be observed in the red blood cells. (credit: modification of work by Centers for Disease Control and Prevention)

## Chagas Disease

Also called American trypanosomiasis, Chagas disease is a zoonosis classified as a neglected tropical disease(NTD). It is caused by the flagellated protozoan *Trypanosoma cruzi* and is most commonly transmitted to animals and people through the feces of triatomine bugs. The triatomine bug is nicknamed the kissing bug because it frequently bites humans on the face or around the eyes; the insect often defecates near the bite and the infected fecal matter may be rubbed into the bite wound by the bitten individual (Figure 15.2.6). The bite itself is painless and, initially, many people show no signs of the disease. Alternative modes of transmission include contaminated blood transfusions, organ transplants from infected donors, and congenital transmission from mother to fetus.

Chagas disease is endemic throughout much of Mexico, Central America, and South America, where, according to WHO, an estimated 6 million to 7 million people are infected.[7] Currently, Chagas disease is not endemic in the US, even though triatomine bugs are found in the southern half of the country.

Triatomine bugs typically are active at night, when they take blood meals by biting the faces and lips of people or animals as they sleep and often defecate near the site of the bite. Infection occurs when the host rubs the feces into their eyes, mouth, the bite wound, or another break in the skin. The protozoan then enters the blood and invades tissues of the heart and central nervous system, as well as macrophages and monocytes. Nonhuman reservoirs of *T. cruzi* parasites include wild animals and domesticated animals such as dogs and cats, which also act as reservoirs of the pathogen.[8]

There are three phases of Chagas disease: acute, intermediate, and chronic. These phases can be either asymptomatic or life-threatening depending on the immunocompetence status of the patient.

In acute phase disease, symptoms include fever, headache, myalgia, rash, vomiting, diarrhea, and enlarged spleen, liver, and lymph nodes. In addition, a localized nodule called a chagoma may form at the portal of entry, and swelling of the eyelids or the side of the face, called Romaña's sign, may occur near the bite wound. Symptoms of the acute phase may resolve spontaneously, but if untreated, the infection can persist in tissues, causing irreversible damage to the heart or brain. In rare cases, young

children may die of myocarditis or meningoencephalitis during the acute phase of Chagas disease.

Following the acute phase is a prolonged intermediate phase during which few or no parasites are found in the blood and most people are asymptomatic. Many patients will remain asymptomatic for life; however, decades after exposure, an estimated 20%–30% of infected people will develop chronic disease that can be debilitating and sometimes life threatening. In the chronic phase, patients may develop painful swelling of the colon, leading to severe twisting, constipation, and bowel obstruction; painful swelling of the esophagus, leading to dysphagia and malnutrition; and flaccid cardiomegaly (enlargement of the heart), which can lead to heart failure and sudden death.

Diagnosis can be confirmed through several different tests, including direct microscopic observation of trypanosomes in the blood, IFA, EIAs, PCR, and culturing in artificial media. In endemic regions, xenodiagnoses may be used; this method involves allowing uninfected kissing bugs to feed on the patient and then examining their feces for the presence of *T. cruzi*.

The medications nifurtimox and benznidazole are effective treatments during the acute phase of Chagas disease. The efficacy of these drugs is much lower when the disease is in the chronic phase. Avoiding exposure to the pathogen through vector control is the most effective method of limiting this disease.

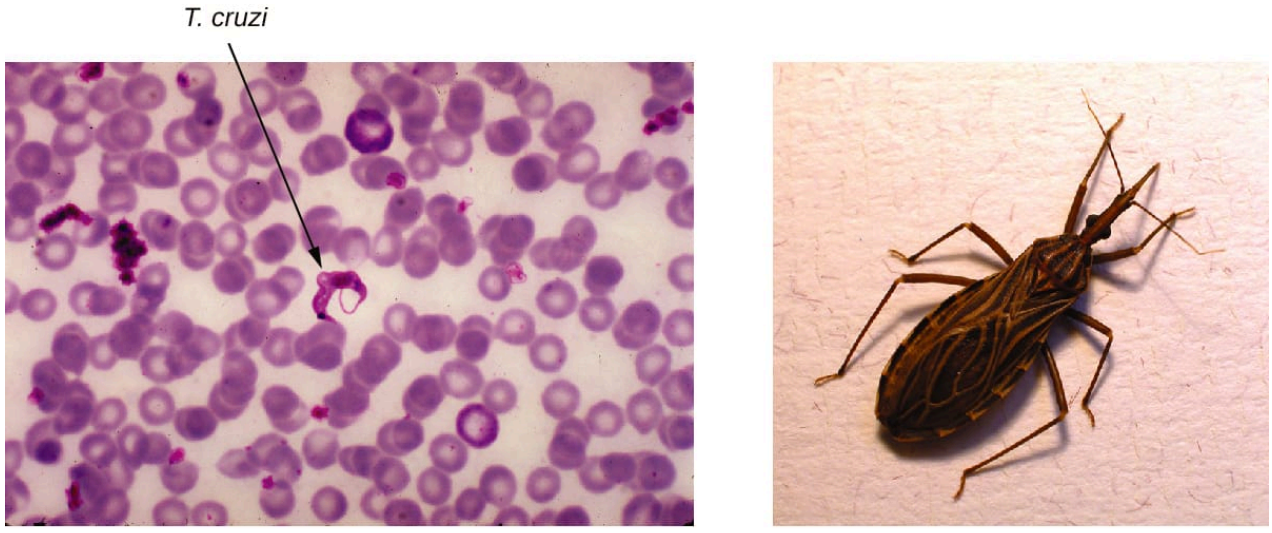



Figure 15.2.6: (a) *Trypanosoma cruzi* protozoan in a blood smear from a patient with Chagas disease. (b) The triatomine bug (also known as the kissing bug or assassin bug) is the vector of Chagas disease. (credit a: modification of work by Centers for Disease Control and Prevention; credit b: modification of work by Erwin Huebner)

**Exercise 15.2.3**

How do kissing bugs infect humans with *Trypanosoma cruzi*?

## Leishmaniasis

Although it is classified as an NTD, leishmaniasis is relatively widespread in tropical and subtropical regions, affecting people in more than 90 countries. It is caused by approximately 20 different species of *Leishmania*, protozoan parasites that are transmitted by sand fly vectors such as *Phlebotomus* spp. and *Lutzomyia* spp. Dogs, cats, sheep, horses, cattle rodents, and humans can all serve as reservoirs.

The *Leishmania* protozoan is phagocytosed by macrophages but uses virulence factors to avoid destruction within the phagolysosome. The virulence factors inhibit the phagolysosome enzymes that would otherwise destroy the parasite. The parasite reproduces within the macrophage, lyses it, and the progeny infect new macrophages (see Micro Connections: When Phagocytosis Fails).

The three major clinical forms of leishmaniasis are cutaneous (oriental sore, Delhi boil, Aleppo boil), visceral (kala-azar, Dumdum

fever), and mucosal (espundia). The most common form of disease is cutaneous leishmaniasis, which is characterized by the formation of sores at the site of the insect bite that may start out as papules or nodules before becoming large ulcers (Figure 15.2.7).

It may take visceral leishmaniasis months and sometimes years to develop, leading to enlargement of the lymph nodes, liver, spleen, and bone marrow. The damage to these body sites triggers fever, weight loss, and swelling of the spleen and liver. It also causes a decrease in the number of red blood cells (anemia), white blood cells (leukopenia), and platelets (thrombocytopenia), causing the patient to become immunocompromised and more susceptible to fatal infections of the lungs and gastrointestinal tract.

The mucosal form of leishmaniasis is one of the less common forms of the disease. It causes a lesion similar to the cutaneous form but mucosal leishmaniasis is associated with mucous membranes of the mouth, nares, or pharynx, and can be destructive and disfiguring. Mucosal leishmaniasis occurs less frequently when the original cutaneous (skin) infection is promptly treated.

Definitive diagnosis of leishmaniasis is made by visualizing organisms in Giemsa-stained smears, by isolating *Leishmania* protozoans in cultures, or by PCR-based assays of aspirates from infected tissues. Specific DNA probes or analysis of cultured parasites can help to distinguish *Leishmania* species that are causing simple cutaneous leishmaniasis from those capable of causing mucosal leishmaniasis.

Cutaneous leishmaniasis is usually not treated. The lesions will resolve after weeks (or several months), but may result in scarring. Recurrence rates are low for this disease. More serious infections can be treated with stibogluconate(antimony gluconate), amphotericin B, and miltefosine.

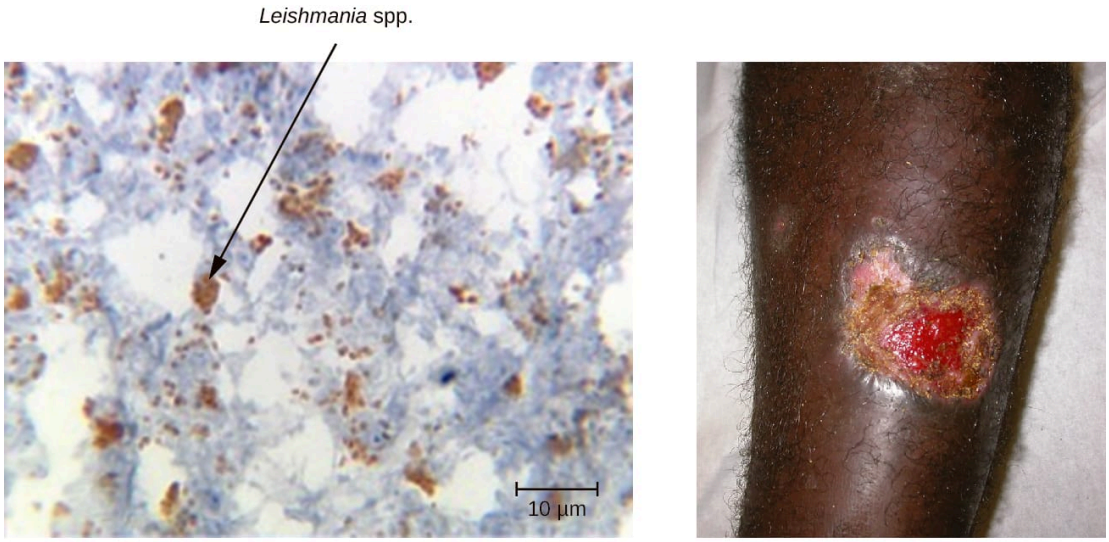



Figure 15.2.7: (a) A micrograph of a tissue sample from a patient with localized cutaneous leishmaniasis. Parasitic *Leishmania mexicana* (black arrow) are visible in and around the host cells. (b) Large skin ulcers are associated with cutaneous leishmaniasis. (credit a: modification of work by Fernández-Figueroa EA, Rangel-Escareño C, Espinosa-Mateos V, Carrillo-Sánchez K, Salaiza-Suazo N, Carrada-Figueroa G, March-Mifsut S, and Becker I; credit b: modification of work by Jean Fortunet)

**Exercise 15.2.4**

Compare the mucosal and cutaneous forms of leishmaniasis.

## Schistosomiasis

Schistosomiasis (bilharzia) is an NTD caused by blood flukes in the genus *Schistosoma* that are native to the Caribbean, South America, Middle East, Asia, and Africa. Most human schistosomiasis cases are caused by *Schistosoma mansoni, S. haematobium*, or *S. japonicum*. *Schistosoma* are the only trematodes that invade through the skin; all other trematodes infect by ingestion. WHO estimates that at least 258 million people required preventive treatment for schistosomiasis in 2014.[9]

Infected human hosts shed *Schistosoma* eggs in urine and feces, which can contaminate freshwater habitats of snails that serve as intermediate hosts. The eggs hatch in the water, releasing miracidia, an intermediate growth stage of the *Schistosoma* that infect the snails. The miracidia mature and multiply inside the snails, transforming into cercariae that leave the snail and enter the water, where they can penetrate the skin of swimmers and bathers. The cercariae migrate through human tissue and enter the bloodstream, where they mature into adult male and female worms that mate and release fertilized eggs. The eggs travel through the bloodstream and penetrate various body sites, including the bladder or intestine, from which they are excreted in urine or stool to start the life cycle over again (Figure 3.2.4).

A few days after infection, patients may develop a rash or itchy skin associated with the site of cercariae penetration. Within 1–2 months of infection, symptoms may develop, including fever, chills, cough, and myalgia, as eggs that are not excreted circulate through the body. After years of infection, the eggs become lodged in tissues and trigger inflammation and scarring that can damage the liver, central nervous system, intestine, spleen, lungs, and bladder. This may cause abdominal pain, enlargement of the liver, blood in the urine or stool, and problems passing urine. Increased risk for bladder cancer is also associated with chronic *Schistosoma* infection. In addition, children who are repeatedly infected can develop malnutrition, anemia, and learning difficulties.

Diagnosis of schistosomiasis is made by the microscopic observation of eggs in feces or urine, intestine or bladder tissue specimens, or serologic tests. The drug praziquantel is effective for the treatment of all schistosome infections. Improving wastewater management and educating at-risk populations to limit exposure to contaminated water can help control the spread of the disease.

## Cercarial Dermatitis

The cercaria of some species of *Schistosoma* can only transform into adult worms and complete their life cycle in animal hosts such as migratory birds and mammals. The cercaria of these worms are still capable of penetrating human skin, but they are unable to establish a productive infection in human tissue. Still, the presence of the cercaria in small blood vessels triggers an immune response, resulting in itchy raised bumps called cercarial dermatitis (also known as swimmer's itch or clam digger's itch). Although it is uncomfortable, cercarial dermatitis is typically self-limiting and rarely serious. Antihistamines and antipruritics can be used to limit inflammation and itching, respectively.

**Exercise 15.2.5**

How do schistosome infections in humans occur?

**Disease Profile**

**Common Eukaryotic Pathogens of the Human Circulatory System**

Protozoan and helminthic infections are prevalent in the developing world. A few of the more important parasitic infections are summarized in Figure 15.2.8.

| Parasitic Diseases of the Circulatory and Lymphatic Systems | | | | | |
|---|---|---|---|---|---|
| **Disease** | **Pathogen** | **Signs and Symptoms** | **Transmission** | **Diagnostic Tests** | **Antimicrobial Drugs** |
| **Protozoa** | | | | | |
| Babesiosis | *Babesia* spp. | Malaise, chills, fever, headache, myalgia, arthralgia | From animals to humans via *Ixodes* tick vectors | Blood smear, serology, IFA, and PCR | Atovaquone and azithromycin or clindamycin and quinine |
| Chagas disease | *Trypanosoma cruzi* | Fever, headache, body aches, swollen lymph nodes; potentially fatal | Between humans or from animal reservoirs via triatomine (kissing bug) vector | Blood smear, IFA, EIA, PCR, xenodiagnosis | Nifurtimox, benznidazole |
| Leishmaniasis | *Leishmania* spp. | Ulcer; enlargement of the lymph nodes, liver, spleen, and other organs | Between humans or from animal reservoirs via sand fly (*Phlebotomus* spp., *Lutzomyia* spp.) vectors | Blood smear, culture, PCR, DNA probe, biopsy | Stibogluconate, amphotericin B. |
| Malaria | *Plasmodium vivax*, *P. malariae*, *P. falciparum*, *P. ovale*, *P. knowlesi* | Extreme fever, chills, myalgia, nausea, and vomiting, possibly leading to organ failure and death | Between humans via *Anopheles* mosquito vectors | Blood smear, EIA | Chloroquine, atovaquone, artemether, and lumefantrine |
| Toxoplasmosis | *Toxoplasma gondii* | Tissue cysts; in pregnant women, birth defects or miscarriage | Contact with feces of infected cat; eating contaminated vegetables or undercooked meat of infected animal | Serological tests, direct detection of pathogen in tissue sections | Sulfadiazine, pyrimethamine, spiramycin |
| **Helminths** | | | | | |
| Schistosomiasis | *Schistosoma* spp. | Rash, fever, chills, myalgia; chronic inflammation and scarring of liver, spleen, and other organs where cysts develop | Snail hosts release cercaria into freshwater; cercaria burrow into skin of swimmers and bathers | Eggs in stool or urine, tissue biopsy, serological testing | Praziquantel |

Figure 15.2.8: Parasitic diseases of the Circulatory and Lymphatic systems.

## Clinical Focus

**Resolution**

Despite continued antibiotic treatment and the removal of the venous catheter, Barbara's condition further declined. She began to show signs of shock and her blood pressure dropped to 77/50 mmHg. Anti-inflammatory drugs and drotrecogin-α were administered to combat sepsis. However, by the seventh day of hospitalization, Barbara experienced hepatic and renal failure and died.

*Staphylococcus aureus* most likely formed a biofilm on the surface of Barbara's catheter. From there, the bacteria were chronically shed into her circulation and produced the initial clinical symptoms. The chemotherapeutic therapies failed in large part because of the drug-resistant MRSA isolate. Virulence factors like leukocidin and hemolysins also interfered with her immune response. Barbara's ultimate decline may have been a consequence of the production of enterotoxins and toxic shock syndrome toxin (TSST), which can initiate toxic shock.

Venous catheters are common life-saving interventions for many patients requiring long-term administration of medication or fluids. However, they are also common sites of bloodstream infections. The World Health Organization estimates that there are up to 80,000 catheter-related bloodstream infections each year in the US, resulting in about 20,000 deaths.[10]

Go back to the previous Clinical Focus box.

# Key Concepts and Summary

- **Malaria** is a protozoan parasite that remains an important cause of death primarily in the tropics. Several species in the genus *Plasmodium* are responsible for malaria and all are transmitted by *Anopheles* mosquitoes. *Plasmodium* infects and destroys human red blood cells, leading to organ damage, anemia, blood vessel necrosis, and death. Malaria can be treated with various antimalarial drugs and prevented through vector control.
- **Toxoplasmosis** is a widespread protozoal infection that can cause serious infections in the immunocompromised and in developing fetuses. Domestic cats are the definitive host.
- Babesiosis is a generally asymptomatic infection of red blood cells that can causes malaria-like symptoms in elderly, immunocompromised, or asplenic patients.
- **Chagas disease** is a tropical disease transmitted by triatomine bugs. The trypanosome infects heart, neural tissues, monocytes, and phagocytes, often remaining latent for many years before causing serious and sometimes fatal damage to the digestive system and heart.
- **Leishmaniasis** is caused by the protozoan *Leishmania* and is transmitted by sand flies. Symptoms are generally mild, but

serious cases may cause organ damage, anemia, and loss of immune competence.
- **Schistosomiasis** is caused by a fluke transmitted by snails. The fluke moves throughout the body in the blood stream and chronically infects various tissues, leading to organ damage.

## Footnotes


1. World Health Organization. “World Malaria Report 2015: Summary.” 2015. http://www.who.int/malaria/publicati...015/report/en/. Accessed July 28, 2016.
2. A.M. Tenter et al.. “*Toxoplasma gondii*: From Animals to Humans.” *International Journal for Parasitology* 30 no. 12-13 (2000):1217–1258.
3. Centers for Disease Control and Prevention. “Parasites - Toxoplasmosis (Toxoplasma Infection). Epidemiology & Risk Factors.” 2015 http://www.cdc.gov/parasites/toxoplasmosis/epi.html. Accessed July 28, 2016.
4. J. Flegr. “Effects of *Toxoplasma* on Human Behavior.” *Schizophrenia Bulletin* 33, no. 3 (2007):757–760.
5. Ibid
6. Centers for Disease Control and Prevention. “Parasites - Toxoplasmosis (Toxoplasma infection). Toxoplasmosis Frequently Asked Questions (FAQs).” 2013. http://www.cdc.gov/parasites/toxopla...info/faqs.html. Accessed July 28, 2016.
7. World Health Organization. “Chagas disease (American trypanosomiasis). Fact Sheet.” 2016. http://www.who.int/mediacentre/factsheets/fs340/en/. Accessed July 29, 2016.
8. C.E. Reisenman et al. “Infection of Kissing Bugs With *Trypanosoma cruzi*, Tucson, Arizona, USA.” *Emerging Infectious Diseases* 16 no. 3 (2010):400–405.
9. World Health Organization. “Schistosomiasis. Fact Sheet.” 2016. http://www.who.int/mediacentre/factsheets/fs115/en/. Accessed July 29, 2016.
10. World Health Organization. “Patient Safety, Preventing Bloodstream Infections From Central Line Venous Catheters.” 2016. www.who.int/patientsafety/imp...tation/bsi/en/. Accessed July 29, 2016.


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# 15.3: Review Questions

## Multiple Choice

1. Which of the following diseases is caused by a helminth?
   A. leishmaniasis
   B. malaria
   C. Chagas disease
   D. schistosomiasis

*Answer available at the end of this section.*

2. Which of these is the most common form of leishmaniasis?
   A. cutaneous
   B. mucosal
   C. visceral
   D. intestinal

*Answer available at the end of this section.*

3. Which of the following is a causative agent of malaria?
   A. *Trypanosoma cruzi*
   B. *Toxoplasma gondii*
   C. *Plasmodium falciparum*
   D. *Schistosoma mansoni*

*Answer available at the end of this section.*

4. Which of the following diseases does not involve an arthropod vector?
   A. schistosomiasis
   B. malaria
   C. Chagas disease
   D. babesiosis

*Answer available at the end of this section.*

## Fill in the Blank

5. _____ are transmitted by vectors such as ticks or mosquitoes.

*Answer available at the end of this section.*

6. The _____ mosquito is the biological vector for malaria.

*Answer available at the end of this section.*

7. The kissing bug is the biological vector for _____.

*Answer available at the end of this section.*

8. Cercarial dermatitis is also known as _____.

*Answer available at the end of this section.*

## Short Answer

9. Describe main cause of *Plasmodium falciparum* infection symptoms.
10. Why should pregnant women avoid cleaning their cat's litter box or do so with protective gloves?

## Critical Thinking

11. What measures can be taken to reduce the likelihood of malaria reemerging in the US?

## Answers

**Multiple Choice**
D

**Multiple Choice**
A

**Multiple Choice**
C

**Multiple Choice**
A

**Fill in the Blank**
Arboviruses

**Fill in the Blank**
*Anopheles*

**Fill in the Blank**
Chagas disease

**Fill in the Blank**
swimmer's itch

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# 15: CIRCULATORY AND LYMPHATIC SYSTEM INFECTIONS (PART A)

Yellow fever was once common in the southeastern US, with annual outbreaks of more than 25,000 infections in New Orleans in the mid-1800s.[1] In the early 20th century, efforts to eradicate the virus that causes yellow fever were successful thanks to vaccination programs and effective control (mainly through the insecticide dichlorodiphenyltrichloroethane [DDT]) of *Aedes aegypti*, the mosquito that serves as a vector. Today, the virus has been largely eradicated in North America.

Elsewhere, efforts to contain yellow fever have been less successful. Despite mass vaccination campaigns in some regions, the risk for yellow fever epidemics is rising in dense urban cities in Africa and South America.[2] In an increasingly globalized society, yellow fever could easily make a comeback in North America, where *A. aegypti* is still present. If these mosquitoes were exposed to infected individuals, new outbreaks would be possible.

Like yellow fever, many of the circulatory and lymphatic diseases discussed in this chapter are emerging or re-emerging worldwide. Despite medical advances, diseases like malaria, Ebola, and others could become endemic in the US given the right circumstances.

## Chapter Outline

15.1: Arthropod-Borne Viral Diseases

15.2: Parasitic Infections of the Circulatory and Lymphatic Systems

15.3: Review Questions

## Footnotes

1. Centers for Disease Control and Prevention. “The History of Yellow Fever.” http://www.cdc.gov/travel-training/local/HistoryEpidemiologyandVaccination/page27568.html
2. C.L. Gardner, K.D. Ryman. “Yellow Fever: A Reemerging Threat.” *Clinical Laboratory Medicine* 30 no. 1 (2010):237–260.

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# WEEK 11

## 16: Circulatory and Lymphatic System Infections (Part B)

16.1: Bacterial Infections of the Circulatory and Lymphatic Systems
16.2: Review Questions

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# 16.1: Bacterial Infections of the Circulatory and Lymphatic Systems

**Learning Objectives**

- Identify and compare bacteria that most commonly cause infections of the circulatory and lymphatic systems
- Compare the major characteristics of specific bacterial diseases affecting the circulatory and lymphatic systems

Bacteria can enter the circulatory and lymphatic systems through acute infections or breaches of the skin barrier or mucosa. Breaches may occur through fairly common occurrences, such as insect bites or small wounds. Even the act of tooth brushing, which can cause small ruptures in the gums, may introduce bacteria into the circulatory system. In most cases, the bacteremia that results from such common exposures is transient and remains below the threshold of detection. In severe cases, bacteremia can lead to septicemia with dangerous complications such as toxemia, sepsis, and septic shock. In these situations, it is often the immune response to the infection that results in the clinical signs and symptoms rather than the microbes themselves.

## Epidemic Typhus

The disease epidemic typhus is caused by *Rickettsia prowazekii* and is transmitted by body lice, *Pediculus humanus*. Flying squirrels are animal reservoirs of *R. prowazekii* in North America and can also be sources of lice capable of transmitting the pathogen. Epidemic typhus is characterized by a high fever and body aches that last for about 2 weeks. A rash develops on the abdomen and chest and radiates to the extremities. Severe cases can result in death from shock or damage to heart and brain tissues. Infected humans are an important reservoir for this bacterium because *R. prowazekii* is the only *Rickettsia* that can establish a chronic carrier state in humans.

Epidemic typhus has played an important role in human history, causing large outbreaks with high mortality rates during times of war or adversity. During World War I, epidemic typhus killed more than 3 million people on the Eastern front.[18] With the advent of effective insecticides and improved personal hygiene, epidemic typhus is now quite rare in the US. In the developing world, however, epidemics can lead to mortality rates of up to 40% in the absence of treatment.[19] In recent years, most outbreaks have taken place in Burundi, Ethiopia, and Rwanda. For example, an outbreak in Burundi refugee camps in 1997 resulted in 45,000 illnesses in a population of about 760,000 people.[20]

A rapid diagnosis is difficult because of the similarity of the primary symptoms with those of many other diseases. Molecular and immunohistochemical diagnostic tests are the most useful methods for establishing a diagnosis during the acute stage of illness when therapeutic decisions are critical. PCR to detect distinctive genes from *R. prowazekii* can be used to confirm the diagnosis of epidemic typhus, along with immunofluorescent staining of tissue biopsy specimens. Serology is usually used to identify rickettsial infections. However, adequate antibody titers take up to 10 days to develop. Antibiotic therapy is typically begun before the diagnosis is complete. The most common drugs used to treat patients with epidemic typhus are doxycycline or chloramphenicol.

## Rocky Mountain Spotted Fever

The disease Rocky Mountain spotted fever (RMSF) is caused by *Rickettsia rickettsii* and is transmitted by the bite of a hard-bodied tick such as the American dog tick (*Dermacentor variabilis*), Rocky Mountain wood tick (*D. andersoni*), or brown dog tick (*Rhipicephalus sanguineus*).

This disease is endemic in North and South America and its incidence is coincident with the arthropod vector range. Despite its name, most cases in the US do not occur in the Rocky Mountain region but in the Southeast; North Carolina, Oklahoma, Arkansas, Tennessee, and Missouri account for greater than 60% of all cases.[21] The map in Figure 16.1.7 shows the distribution of prevalence in the US in 2010.

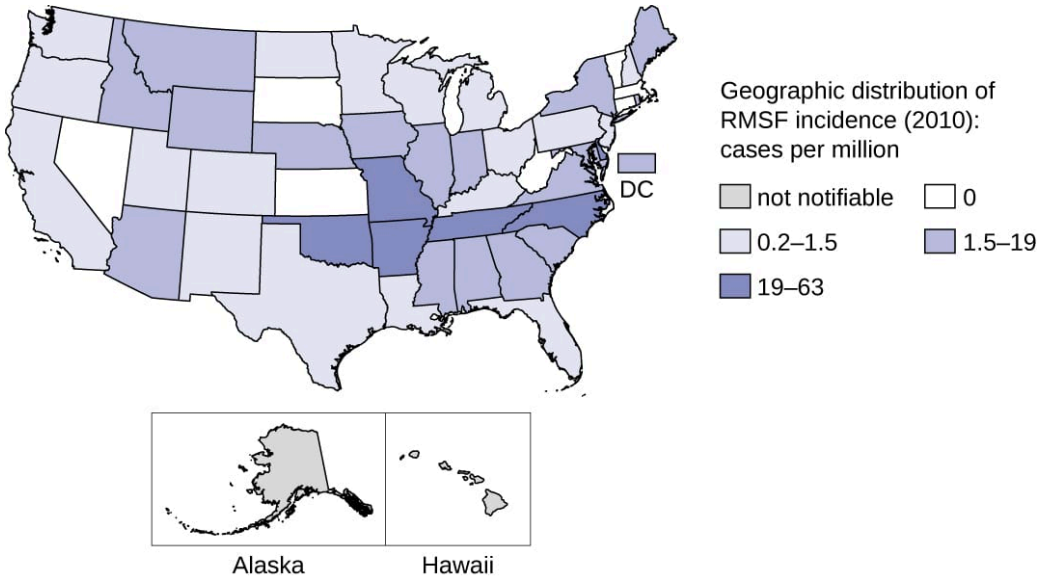



Figure 16.1.7: In the US, Rocky Mountain spotted fever is most prevalent in the southeastern states. (credit: modification of work by Centers for Disease Control and Prevention)

Signs and symptoms of RMSF include a high fever, headache, body aches, nausea, and vomiting. A petechial rash(similar in appearance to measles) begins on the hands and wrists, and spreads to the trunk, face, and extremities (Figure 16.1.8). If untreated, RMSF is a serious illness that can be fatal in the first 8 days even in otherwise healthy patients. Ideally, treatment should begin before petechiae develop, because this is a sign of progression to severe disease; however, the rash usually does not appear until day 6 or later after onset of symptoms and only occurs in 35%–60% of patients with the infection. Increased vascular permeability associated with petechiae formation can result in fatality rates of 3% or greater, even in the presence of clinical support. Most deaths are due to hypotension and cardiac arrest or from ischemia following blood coagulation.

Diagnosis can be challenging because the disease mimics several other diseases that are more prevalent. The diagnosis of RMSF is made based on symptoms, fluorescent antibody staining of a biopsy specimen from the rash, PCR for *Rickettsia rickettsii*, and acute and convalescent serologic testing. Primary treatment is doxycycline, with chloramphenicol as the second choice.



Figure 16.1.8: Rocky Mountain spotted fever causes a petechial rash. Unlike epidemic or murine typhus, the rash begins at the hands and wrists and then spreads to the trunk. (credit: modification of work by Centers for Disease Control and Prevention)

# Lyme Disease

Lyme disease is caused by the spirochete *Borrelia burgdorferi* that is transmitted by the bite of a hard-bodied, black-legged *Ixodes* tick. *I. scapularis* is the biological vector transmitting *B. burgdorferi* in the eastern and north-central US and *I. pacificus* transmits *B. burgdorferi* in the western US (Figure 16.1.10). Different species of *Ixodes* ticks are responsible for *B. burgdorferi* transmission in Asia and Europe. In the US, Lyme disease is the most commonly reported vectorborne illness. In 2014, it was the fifth most common Nationally Notifiable disease.[22]

*Ixodes* ticks have complex life cycles and deer, mice, and even birds can act as reservoirs. Over 2 years, the ticks pass through four developmental stages and require a blood meal from a host at each stage. In the spring, tick eggs hatch into six-legged larvae. These larvae do not carry *B. burgdorferi* initially. They may acquire the spirochete when they take their first blood meal (typically from a mouse). The larvae then overwinter and molt into eight-legged nymphs in the following spring. Nymphs take blood meals primarily from small rodents, but may also feed on humans, burrowing into the skin. The feeding period can last several days to a week, and it typically takes 24 hours for an infected nymph to transmit enough *B. burgdorferi* to cause infection in a human host. Nymphs ultimately mature into male and female adult ticks, which tend to feed on larger animals like deer or, occasionally, humans. The adults then mate and produce eggs to continue the cycle (Figure 16.1.9).

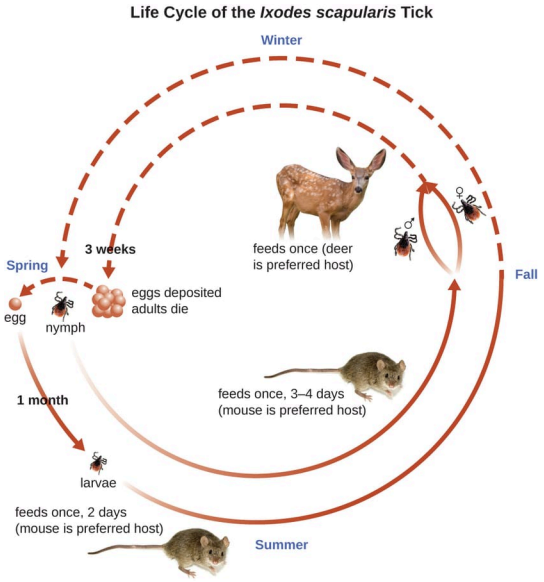



Figure 16.1.9: This image shows the 2-year life cycle of the black-legged tick, the biological vector of Lyme disease. (credit “mouse”: modification of work by George Shuklin)

The symptoms of Lyme disease follow three stages: early localized, early disseminated, and late stage. During the early-localized stage, approximately 70%–80%[23] of cases may be characterized by a bull's-eye rash, called erythema migrans, at the site of the initial tick bite. The rash forms 3 to 30 days after the tick bite (7 days is the average) and may also be warm to the touch (Figure 16.1.10).[24] This diagnostic sign is often overlooked if the tick bite occurs on the scalp or another less visible location. Other early symptoms include flu-like symptoms such as malaise, headache, fever, and muscle stiffness. If the patient goes untreated, the second early-disseminated stage of the disease occurs days to weeks later. The symptoms at this stage may include severe headache, neck stiffness, facial paralysis, arthritis, and carditis. The late-stage manifestations of the disease may occur years after exposure. Chronic inflammation causes damage that can eventually cause severe arthritis, meningitis, encephalitis, and altered mental states. The disease may be fatal if untreated.

A presumptive diagnosis of Lyme disease can be made based solely on the presence of a bull’s-eye rash at the site of infection, if it is present, in addition to other associated symptoms (Figure 16.1.10). In addition, indirect immunofluorescent antibody (IFA) labeling can be used to visualize bacteria from blood or skin biopsy specimens. Serological tests like ELISA can also be used to detect serum antibodies produced in response to infection. During the early stage of infection (about 30 days), antibacterial drugs such as amoxicillin and doxycycline are effective. In the later stages, penicillin G, chloramphenicol, or ceftriaxone can be given intravenously.

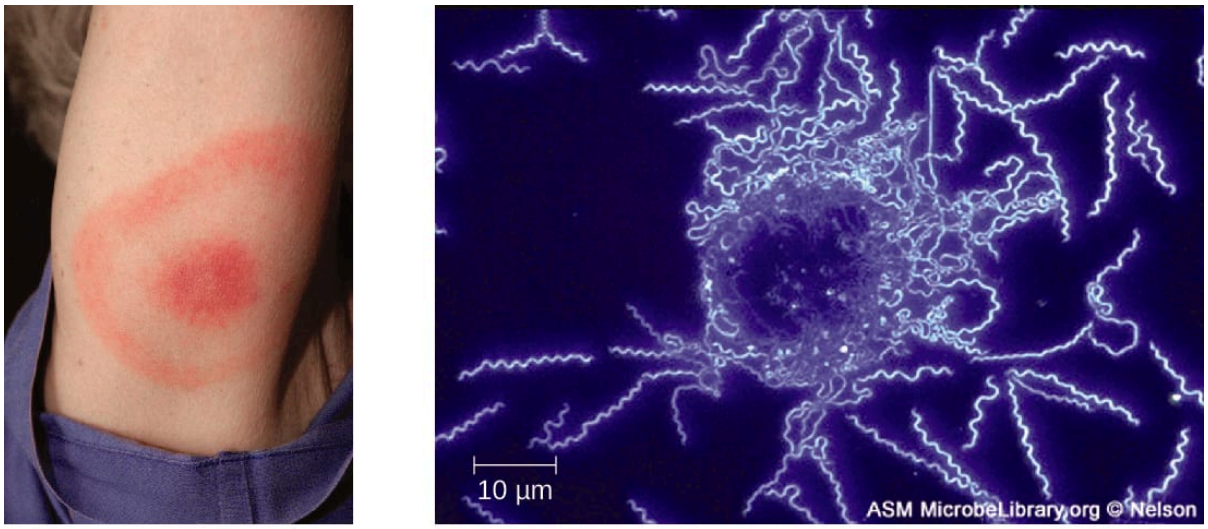



Figure 16.1.10: (a) A characteristic bull's eye rash of Lyme disease forms at the site of a tick bite. (b) A darkfield micrograph shows *Borrelia burgdorferi*, the causative agent of Lyme disease. (credit a: modification of work by Centers for Disease Control and Prevention; credit b: modification of work by American Society for Microbiology)

## Relapsing Fever

*Borrelia* spp. also can cause relapsing fever. Two of the most common species are *B. recurrentis*, which causes epidemics of louseborne relapsing fever, and *B. hermsii*, which causes tickborne relapsing fevers. These *Borrelia* species are transmitted by the body louse *Pediculus humanus* and the soft-bodied tick *Ornithodoros hermsi*, respectively. Lice acquire the spirochetes from human reservoirs, whereas ticks acquire them from rodent reservoirs. Spirochetes infect humans when *Borrelia* in the vector's saliva or excreta enter the skin rapidly as the vector bites.

In both louse- and tickborne relapsing fevers, bacteremia usually occurs after the initial exposure, leading to a sudden high fever (39–43 °C [102.2–109.4 °F) typically accompanied by headache and muscle aches. After about 3 days, these symptoms typically subside, only to return again after about a week. After another 3 days, the symptoms subside again but return a week later, and this cycle may repeat several times unless it is disrupted by antibiotic treatment. Immune evasion through bacterial antigenic variation is responsible for the cyclical nature of the symptoms in these diseases.

The diagnosis of relapsing fever can be made by observation of spirochetes in blood, using darkfield microscopy (Figure 16.1.11). For louseborne relapsing fever, doxycycline or erythromycin are the first-line antibiotics. For tickborne relapsing fever, tetracycline or erythromycin are the first-line antibiotics.

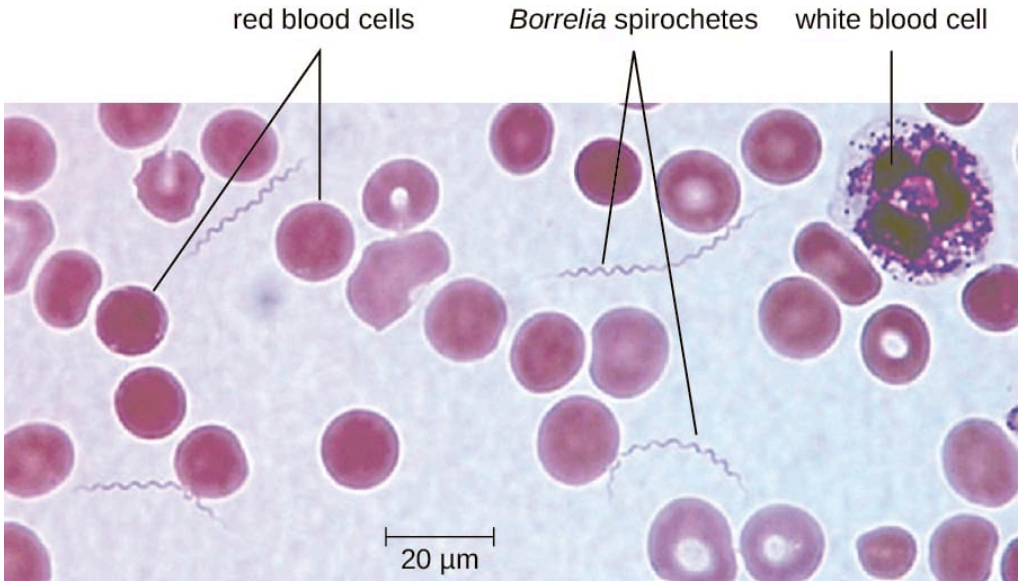



Figure 16.1.11: A peripheral blood smear from a patient with tickborne relapsing fever. *Borrelia* appears as thin spirochetes among the larger red blood cells. (credit: modification of work by Centers for Disease Control and Prevention)

## Key Concepts and Summary

- Bacterial infections of the circulatory system are almost universally serious. Left untreated, most have high mortality rates.
- Bacterial pathogens usually require a breach in the immune defenses to colonize the circulatory system. Most often, this involves a wound or the bite of an arthropod vector, but it can also occur in hospital settings and result in nosocomial infections.
- **Epidemic typhus, Rocky Mountain spotted fever, Lyme disease,** and **relapsing fever** are transmitted by arthropod vectors.
- Because their symptoms are so similar to those of other diseases, many bacterial infections of the circulatory system are difficult to diagnose.
- Standard antibiotic therapies are effective for the treatment of most bacterial infections of the circulatory system, unless the bacterium is resistant, in which case synergistic treatment may be required.
- The systemic immune response to a bacteremia, which involves the release of excessive amounts of cytokines, can sometimes be more damaging to the host than the infection itself.

## Footnotes

1. S.P. LaRosa. “Sepsis.” 2010. http://www.clevelandclinicmeded.com/...isease/sepsis/.
2. D.C. Angus, T. Van der Poll. “Severe Sepsis and Septic Shock.” *New England Journal of Medicine* 369, no. 9 (2013):840–851.
3. Centers for Disease Control and Prevention. “Toxic Shock Syndrome (Other Than Streptococcal) (TSS) 2011 Case Definition.” https://wwwn.cdc.gov/nndss/condition...finition/2011/. Accessed July 25, 2016.
4. Centers for Disease Control and Prevention. “Streptococcal Toxic Shock Syndrome (STSS) (*Streptococcus pyogenes*) 2010 Case Definition.” https://wwwn.cdc.gov/nndss/condition...finition/2010/. Accessed July 25, 2016.
5. M.E. Shirtliff, Mader JT. “Acute Septic Arthritis.” *Clinical Microbiology Reviews* 15 no. 4 (2002):527–544.
6. J.R. Maneiro et al. “Predictors of Treatment Failure and Mortality in Native Septic Arthritis.” *Clinical Rheumatology* 34, no. 11 (2015):1961–1967.
7. M. Vazquez. “Osteomyelitis in Children.” *Current Opinion in Pediatrics* 14, no. 1 (2002):112–115.
8. A. Beaudoin et al. “Acute Rheumatic Fever and Rheumatic Heart Disease Among Children—American Samoa, 2011–2012.” *Morbidity and Mortality Weekly Report* 64 no. 20 (2015):555–558.
9. M.A. Gerber et al. “Prevention of Rheumatic Fever and Diagnosis and Treatment of Acute Streptococcal Pharyngitis: A Scientific Statement From the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Young, the Interdisciplinary Council on Functional Genomics and Translational Biology, and the Interdisciplinary Council on Quality of Care and Outcomes Research: Endorsed by the American Academy of Pediatrics.” *Circulation* 119, no. 11 (2009):1541–1551.
10. World Health Organization. “WHO Guidelines on Tularaemia.” 2007. http://www.cdc.gov/tularemia/resources/

whotularemiamanual.pdf. Accessed July 26, 2016.
11. MOH Key Laboratory of Systems Biology of Pathogens. "Virulence Factors of Pathogenic Bacteria, *Yersinia*." http://www.mgc.ac.cn/cgi-bin/VFs/gen...Genus=Yersinia. Accessed September 9, 2016.
12. Rosen, William. Justinian's Flea: Plague, Empire, and the Birth of Europe. Viking Adult; pg 3; ISBN 978-0-670-03855-8.
13. Benedictow, Ole J. 2004. The Black Death 1346-1353: The Complete History. Woodbridge: Boydell Press.
14. Centers for Disease Control and Prevention. "Plague: History." http://www.cdc.gov/plague/history/. Accessed September 15, 2016.
15. J.S. Bakken et al. "Diagnosis and Management of Tickborne Rickettsial Diseases: Rocky Mountain Spotted Fever, Ehrlichioses, and Anaplasmosis–United States. A Practical Guide for Physicians and Other Health Care and Public Health Professionals." *MMWR Recommendations and Reports* 55 no. RR04 (2006):1–27.
16. MOH Key Laboratory of Systems Biology of Pathogens, "Virulence Factors of Pathogenic Bacteria, Anaplasma" 2016. http://www.mgc.ac.cn/cgi-bin/VFs/jsif/main.cgi. Accessed July, 26, 2016.
17. Centers for Disease Control and Prevention. "Ehrlichiosis, Symptoms, Diagnosis, and Treatment." 2016. https://www.cdc.gov/ehrlichiosis/symptoms/index.html. Accessed July 29, 2016.
18. Drali, R., Brouqui, P. and Raoult, D. "Typhus in World War I." *Microbiology Today* 41 (2014) 2:58–61.
19. Centers for Disease Control and Prevention. *CDC Health Information for International Travel 2014: The Yellow Book*. Oxford University Press, 2013. http://wwwnc.cdc.gov/travel/yellowbook/2016/infectious-diseases-related-to-travel/rickettsial-spotted-typhus-fevers-related-infections-anaplasmosis-ehrlichiosis. Accessed July 26, 2016.
20. World Health Organization. "Typhus." 1997. www.who.int/mediacentre/factsheets/fs162/en/. Accessed July 26, 2016.
21. Centers for Disease Control and Prevention. "Rocky Mountain Spotted Fever (RMSF): Statistics and Epidemiology." http://www.cdc.gov/rmsf/stats/index.html. Accessed Sept 16, 2016.
22. Centers for Disease Control and Prevention. "Lyme Disease. Data and Statistics." 2015. http://www.cdc.gov/lyme/stats/index.html. Accessed July 26, 2016.
23. Centers for Disease Control and Prevention. "Signs and Symptoms of Untreated Lyme Disease." 2015. http://www.cdc.gov/lyme/signs_symptoms/index.html. Accessed July 27, 2016.
24. Centers for Disease Control and Prevention. "Ticks. Symptoms of Tickborne Illness." 2015. http://www.cdc.gov/ticks/symptoms.html. Accessed July 27, 2016.

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# 16.2: Review Questions

## Multiple Choice

1. Which of the following diseases is caused by a spirochete?
   A. tularemia
   B. relapsing fever
   C. rheumatic fever
   D. Rocky Mountain spotted fever

*Answer available at the end of this section.*

2. Which of the following diseases is transmitted by body lice?
   A. tularemia
   B. bubonic plague
   C. murine typhus
   D. epidemic typhus

*Answer available at the end of this section.*

## Fill in the Blank

3. Lyme disease is characterized by a(n) _____ that forms at the site of infection.

*Answer available at the end of this section.*

## Critical Thinking

4. Why are most vascular pathogens poorly communicable from person to person?

## Answers

**Multiple Choice**

B

**Multiple Choice**

D

**Fill in the Blank**

bull's eye-rash

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# 16: CIRCULATORY AND LYMPHATIC SYSTEM INFECTIONS (PART B)

Yellow fever was once common in the southeastern US, with annual outbreaks of more than 25,000 infections in New Orleans in the mid-1800s.[1] In the early 20th century, efforts to eradicate the virus that causes yellow fever were successful thanks to vaccination programs and effective control (mainly through the insecticide dichlorodiphenyltrichloroethane [DDT]) of *Aedes aegypti*, the mosquito that serves as a vector. Today, the virus has been largely eradicated in North America.

Elsewhere, efforts to contain yellow fever have been less successful. Despite mass vaccination campaigns in some regions, the risk for yellow fever epidemics is rising in dense urban cities in Africa and South America.[2] In an increasingly globalized society, yellow fever could easily make a comeback in North America, where *A. aegypti* is still present. If these mosquitoes were exposed to infected individuals, new outbreaks would be possible.

Like yellow fever, many of the circulatory and lymphatic diseases discussed in this chapter are emerging or re-emerging worldwide. Despite medical advances, diseases like malaria, Ebola, and others could become endemic in the US given the right circumstances.

## Chapter Outline

16.1: Bacterial Infections of the Circulatory and Lymphatic Systems

16.2: Review Questions

## Footnotes

1. Centers for Disease Control and Prevention. “The History of Yellow Fever.” http://www.cdc.gov/travel-training/local/HistoryEpidemiologyandVaccination/page27568.html
2. C.L. Gardner, K.D. Ryman. “Yellow Fever: A Reemerging Threat.” *Clinical Laboratory Medicine* 30 no. 1 (2010):237–260.

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# WEEK 12


## 17: Circulatory and Lymphatic System Infections (Part C)

17.1: Viral Infections of the Circulatory and Lymphatic Systems

17.2: Review Questions


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# 17.1: Viral Infections of the Circulatory and Lymphatic Systems

**Learning Objectives**

- Identify common viral pathogens that cause infections of the circulatory and lymphatic systems
- Compare the major characteristics of specific viral diseases affecting the circulatory and lymphatic systems

Viral pathogens of the circulatory system vary tremendously both in their virulence and distribution worldwide. Some of these pathogens are practically global in their distribution. Fortunately, the most ubiquitous viruses tend to produce the mildest forms of disease. In the majority of cases, those infected remain asymptomatic. On the other hand, other viruses are associated with life-threatening diseases that have impacted human history.

## Ebola Virus Disease

The Ebola virus disease (EVD) is a highly contagious disease caused by species of *Ebolavirus*, a BSL-4 filovirus (Figure 17.1.3 ). Transmission to humans occurs through direct contact with body fluids (e.g., blood, saliva, sweat, urine, feces, or vomit), and indirect contact by contaminated fomites. Infected patients can easily transmit Ebola virus to others if appropriate containment and use of personal protective equipment is not available or used. Handling and working with patients with EVD is extremely hazardous to the general population and health-care workers. In almost every EVD outbreak there have been Ebola infections among health-care workers. This ease of Ebola virus transmission was recently demonstrated in the Ebola epidemic in Guinea, Liberia, and Sierra Leone in 2014, in which more than 28,000 people in 10 countries were infected and more than 11,000 died.[11]

After infection, the initial symptoms of Ebola are unremarkable: fever, severe headache, myalgia, cough, chest pain, and pharyngitis. As the disease progresses, patients experience abdominal pain, diarrhea, and vomiting. Hemorrhaging begins after about 3 days, with bleeding occurring in the gastrointestinal tract, skin, and many other sites. This often leads to delirium, stupor, and coma, accompanied by shock, multiple organ failure, and death. The mortality rates of EVD often range from 50% to 90%.

The initial diagnosis of Ebola is difficult because the early symptoms are so similar to those of many other illnesses. It is possible to directly detect the virus from patient samples within a few days after symptoms begin, using antigen-capture ELISA, immunoglobulin M (IgM) ELISA, PCR, and virus isolation. There are currently no effective, approved treatments for Ebola other than supportive care and proper isolation techniques to contain its spread.

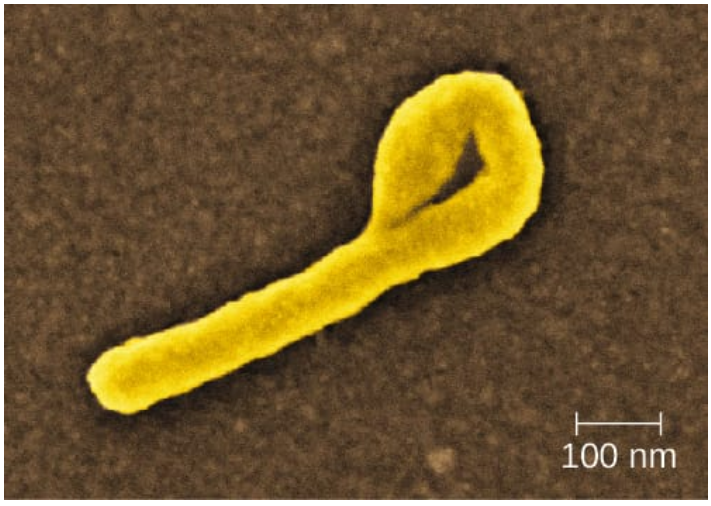



Figure 17.1.3: An Ebola virus particle viewed with electron microscopy. These filamentous viruses often exhibit looped or hooked ends. (credit: modification of work by Centers for Disease Control and Prevention)

**Exercise 17.1.3**

How is Ebola transmitted?

## Hantavirus

The genus *Hantavirus* consists of at least four serogroups with nine viruses causing two major clinical (sometimes overlapping) syndromes: hantavirus pulmonary syndrome (HPS) in North America and hemorrhagic fever with renal syndrome (HFRS) in other continents. Hantaviruses are found throughout the world in wild rodents that shed the virus in their urine and feces. Transmission occurs between rodents and to humans through inhalation of aerosols of the rodent urine and feces. Hantaviruses associated with outbreaks in the US and Canada are transmitted by the deer mouse, white-footed mouse, or cotton rat.

HPS begins as a nonspecific flu-like illness with headache, fever, myalgia, nausea, vomiting, diarrhea, and abdominal pain. Patients rapidly develop pulmonary edema and hypotension resulting in pneumonia, shock, and death, with a mortality rate of up to 50%.[12] This virus can also cause HFRS, which has not been reported in the US. The initial symptoms of this condition include high fever, headache, chills, nausea, inflammation or redness of the eyes, or a rash. Later symptoms are hemorrhaging, hypotension, kidney failure, shock, and death. The mortality rate of HFRS can be as high as 15%.[13]

ELISA, Western blot, rapid immunoblot strip assay (RIBA), and RT-PCR detect host antibodies or viral proteins produced during infection. Immunohistological staining may also be used to detect the presence of viral antigens. There are no clinical treatments other than general supportive care available for HPS infections. Patients with HFRS can be treated with ribavirin.[14]

**Exercise 17.1.4**

Compare the two Hantavirus diseases discussed in this section.

## Key Concepts and Summary

- **Ebola virus disease** is a highly contagious and often fatal infection spread through contact with bodily fluids. Treatments for patients with Ebola virus disease are limited to supportive therapies.
- Vector control and animal reservoir control remain the best defenses against most viruses that cause diseases of the circulatory system.

## Footnotes


1. Centers for Disease Control and Prevention. “Cytomegalovirus (CMV) and Congenital CMV Infection: About CMV.” 2016. www.cdc.gov/cmv/transmission.html. Accessed July 28, 2016.
2. Centers for Disease Control and Prevention. “Cytomegalovirus (CMV) and Congenital CMV Infection: Babies Born with CMV (Congenital CMV Infection).” 2016. http://www.cdc.gov/cmv/congenital-infection.html. Accessed July 28, 2016.
3. ibid.
4. E. Cordero et al. “Cytomegalovirus Disease in Kidney Transplant Recipients: Incidence, Clinical Profile, and Risk Factors.” *Transplantation Proceedings* 44 no. 3 (2012):694–700.
5. L.M. Mofenson et al. “Guidelines for the Prevention and Treatment of Opportunistic Infections Among HIV-Exposed and HIV-Infected Children: Recommendations From CDC, the National Institutes of Health, the HIV Medicine Association of the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the American Academy of Pediatrics.” *MMWR Recommendations and Reports* 58 no. RR-11 (2009):1–166.
6. Centers for Disease Control and Prevention. “History Timeline Transcript.” http://www.cdc.gov/travel-training/local/HistoryEpidemiologyandVaccination/HistoryTimelineTranscript.pdf. Accessed July 28, 2016.
7. Centers for Disease Control and Prevention. “Yellow Fever, Symptoms and Treatment.” 2015 http://www.cdc.gov/yellowfever/symptoms/index.html. Accessed July 28, 2016.
8. J.T. Cathey, J.S. Marr. “Yellow fever, Asia and the East African Slave Trade.” *Transactions of the Royal Society of Tropical Medicine and Hygiene* 108, no. 5 (2014):252–257.

9. Centers for Disease Control and Prevention. “Dengue, Epidemiology.” 2014. http://www.cdc.gov/dengue/epidemiology/index.html. Accessed July 28, 2016.
10. C.R. Pringle “Dengue.” MSD Manual: Consumer Version. https://www.msdmanuals.com/home/infections/viral-infections/dengue. 2016. Accessed Sept 15, 2016.
11. HealthMap. “2014 Ebola Outbreaks.” http://www.healthmap.org/ebola/#timeline. Accessed July 28, 2016.
12. World Health Organization. “Hantavirus Diseases.” 2016. www.who.int/ith/diseases/hantavirus/en/. Accessed July 28, 2016.
13. ibid.
14. Centers for Disease Control and Prevention. “Hantavirus: Treatment.” 2012. http://www.cdc.gov/hantavirus/technical/hps/treatment.html. Accessed July 28, 2016.
15. World Health Organization. “HIV/AIDS: Fact Sheet.” 2016. http://www.who.int/mediacentre/factsheets/fs360/en/. Accessed July 28, 2016.
16. ibid.



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# 17.2: Review Questions

## Multiple Choice

1. Which of these viruses is spread through mouse urine or feces?
   A. Epstein-Barr
   B. hantavirus
   C. human immunodeficiency virus
   D. cytomegalovirus

*Answer available at the end of this section.*

## Critical Thinking

2. Which is a bigger threat to the US population, Ebola or yellow fever? Why?

## Answers

**Multiple Choice**

B

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# 17: CIRCULATORY AND LYMPHATIC SYSTEM INFECTIONS (PART C)

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Elsewhere, efforts to contain yellow fever have been less successful. Despite mass vaccination campaigns in some regions, the risk for yellow fever epidemics is rising in dense urban cities in Africa and South America.[2] In an increasingly globalized society, yellow fever could easily make a comeback in North America, where *A. aegypti* is still present. If these mosquitoes were exposed to infected individuals, new outbreaks would be possible.

Like yellow fever, many of the circulatory and lymphatic diseases discussed in this chapter are emerging or re-emerging worldwide. Despite medical advances, diseases like malaria, Ebola, and others could become endemic in the US given the right circumstances.

## Chapter Outline

17.1: Viral Infections of the Circulatory and Lymphatic Systems

17.2: Review Questions

## Footnotes

1. Centers for Disease Control and Prevention. “The History of Yellow Fever.” http://www.cdc.gov/travel-training/local/HistoryEpidemiologyandVaccination/page27568.html
2. C.L. Gardner, K.D. Ryman. “Yellow Fever: A Reemerging Threat.” *Clinical Laboratory Medicine* 30 no. 1 (2010):237–260.

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# WEEK 13


## 18: Skin and Eye Infections

18.1: Bacterial Infections of the Skin and Eyes

18.2: Review Questions

## 19: Urogenital System Infections

19.1: Bacterial Infections of the Reproductive System

19.2: Review Questions

## 20: Circulatory and Lymphatic System Infections (Part D)

20.1: Bacterial Infections of the Circulatory and Lymphatic Systems

20.2: Viral Infections of the Circulatory and Lymphatic Systems

20.3: Review Questions


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# 18: SKIN AND EYE INFECTIONS

The human body is covered in skin, and like most coverings, skin is designed to protect what is underneath. One of its primary purposes is to prevent microbes in the surrounding environment from invading underlying tissues and organs. But in spite of its role as a protective covering, skin is not itself immune from infection. Certain pathogens and toxins can cause severe infections or reactions when they come in contact with the skin. Other pathogens are opportunistic, breaching the skin's natural defenses through cuts, wounds, or a disruption of normal microbiota resulting in an infection in the surrounding skin and tissue. Still other pathogens enter the body via different routes—through the respiratory or digestive systems, for example—but cause reactions that manifest as skin rashes or lesions.

Nearly all humans experience skin infections to some degree. Many of these conditions are, as the name suggests, "skin deep," with symptoms that are local and non-life-threatening. At some point, almost everyone must endure conditions like acne, athlete's foot, and minor infections of cuts and abrasions, all of which result from infections of the skin. But not all skin infections are quite so innocuous. Some can become invasive, leading to systemic infection or spreading over large areas of skin, potentially becoming life-threatening.

## Chapter Outline

18.1: Bacterial Infections of the Skin and Eyes

18.2: Review Questions

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# 18.1: Bacterial Infections of the Skin and Eyes

**Learning Objectives**

- Identify the most common bacterial pathogens that cause infections of the skin and eyes
- Compare the major characteristics of specific bacterial diseases affecting the skin and eyes

Despite the skin's protective functions, infections are common. Gram-positive *Staphylococcus* spp. are responsible for many of the most common skin infections. However, many skin conditions are not strictly associated with a single pathogen. Opportunistic pathogens of many types may infect skin wounds, and individual cases with identical symptoms may result from different pathogens or combinations of pathogens.

## Staphylococcal Infections of the Skin

*Staphylococcus* species are commonly found on the skin, with *S. epidermidis* and *S. hominis* being prevalent in the normal microbiota. *S. aureus* is also commonly found in the nasal passages and on healthy skin, but pathogenic strains are often the cause of a broad range of infections of the skin and other body systems.

*S. aureus* is quite contagious. It is spread easily through skin-to-skin contact, and because many people are chronic nasal carriers (asymptomatic individuals who carry *S. aureus* in their nares), the bacteria can easily be transferred from the nose to the hands and then to fomites or other individuals. Because it is so contagious, *S. aureus* is prevalent in most community settings. This prevalence is particularly problematic in hospitals, where antibiotic-resistant strains of the bacteria may be present, and where immunocompromised patients may be more susceptible to infection. Resistant strains include methicillin-resistant *S. aureus* (MRSA), which can be acquired through health-care settings (hospital-acquired MRSA, or HA-MRSA) or in the community (community-acquired MRSA, or CA-MRSA). Hospital patients often arrive at health-care facilities already colonized with antibiotic-resistant strains of *S. aureus* that can be transferred to health-care providers and other patients. Some hospitals have attempted to detect these individuals in order to institute prophylactic measures, but they have had mixed success (see Eye on Ethics: Screening Patients for MRSA).

When a staphylococcal infection develops, choice of medication is important. As discussed above, many staphylococci (such as MRSA) are resistant to some or many antibiotics. Thus, antibiotic sensitivity is measured to identify the most suitable antibiotic. However, even before receiving the results of sensitivity analysis, suspected *S. aureus* infections are often initially treated with drugs known to be effective against MRSA, such as trimethoprim-sulfamethoxazole(TMP/SMZ), clindamycin, a tetracycline (doxycycline or minocycline), or linezolid.

The pathogenicity of staphylococcal infections is often enhanced by characteristic chemicals secreted by some strains. Staphylococcal virulence factors include hemolysins called staphylolysins, which are cytotoxic for many types of cells, including skin cells and white blood cells. Virulent strains of *S. aureus* are also coagulase-positive, meaning they produce coagulase, a plasma-clotting protein that is involved in abscess formation. They may also produce leukocidins, which kill white blood cells and can contribute to the production of pus and Protein A, which inhibits phagocytosis by binding to the constant region of antibodies. Some virulent strains of *S. aureus* also produce other toxins, such as toxic shock syndrome toxin-1 (see Virulence Factors of Bacterial and Viral Pathogens).

To confirm the causative agent of a suspected staphylococcal skin infection, samples from the wound are cultured. Under the microscope, gram-positive *Staphylococcus* species have cellular arrangements that form grapelike clusters; when grown on blood agar, colonies have a unique pigmentation ranging from opaque white to cream. A catalase testis used to distinguish *Staphylococcus* from *Streptococcus*, which is also a genus of gram-positive cocci and a common cause of skin infections. *Staphylococcus* species are catalase-positive while *Streptococcus* species are catalase-negative.

Other tests are performed on samples from the wound in order to distinguish coagulase-positive species of *Staphylococcus* (CoPS) such as *S. aureus* from common coagulase-negative species (CoNS) such as *S. epidermidis*. Although CoNS are less likely than CoPS to cause human disease, they can cause infections when they enter the body, as can sometimes occur via catheters, indwelling medical devices, and wounds. Passive agglutination testing can be used to distinguish CoPS from CoNS. If the sample is coagulase-positive, the sample is generally presumed to contain *S. aureus*. Additional genetic testing would be necessary to

identify the particular strain of *S. aureus*.

Another way to distinguish CoPS from CoNS is by culturing the sample on mannitol salt agar (MSA). *Staphylococcus* species readily grow on this medium because they are tolerant of the high concentration of sodium chloride (7.5% NaCl). However, CoPS such as *S. aureus* ferment mannitol (which will be evident on a MSA plate), whereas CoNS such as *S. epidermidis* do not ferment mannitol but can be distinguished by the fermentation of other sugars such as lactose, malonate, and raffinose (Figure 18.1.1).

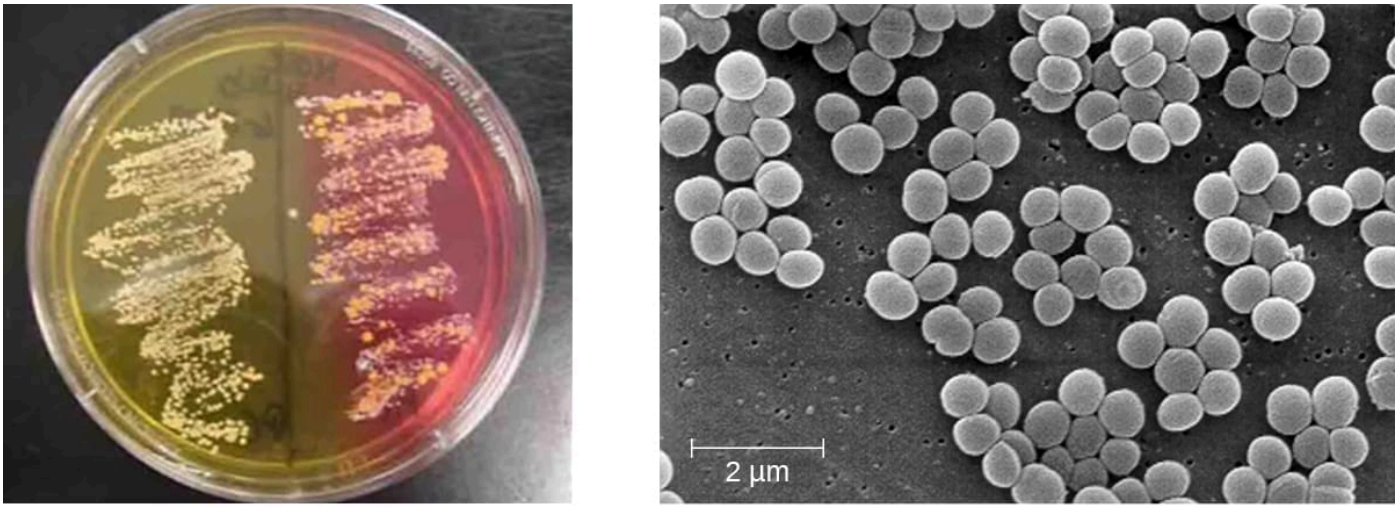



Figure 18.1.1: (a) A mannitol salt agar plate is used to distinguish different species of staphylococci. In this plate, *S. aureus* is on the left and *S. epidermidis* is in the right. Because *S. aureus* is capable of fermenting mannitol, it produces acids that cause the color to change to yellow. (b) This scanning electron micrograph shows the characteristic grapelike clusters of *S. aureus*. (credit a: modification of work by "ScienceProfOnline"/YouTube; credit b: modification of work by Centers for Disease Control and Prevention)

Eye on Ethics

**Screening Patients for MRSA**

According to the CDC, 86% of invasive MRSA infections are associated in some way with healthcare, as opposed to being community-acquired. In hospitals and clinics, asymptomatic patients who harbor MRSA may spread the bacteria to individuals who are more susceptible to serious illness.

In an attempt to control the spread of MRSA, hospitals have tried screening patients for MRSA. If patients test positive following a nasal swab test, they can undergo decolonization using chlorhexidine washes or intranasal mupirocin. Some studies have reported substantial reductions in MRSA disease following implementation of these protocols, while others have not. This is partly because there is no standard protocol for these procedures. Several different MRSA identification tests may be used, some involving slower culturing techniques and others rapid testing. Other factors, such as the effectiveness of general hand-washing protocols, may also play a role in helping to prevent MRSA transmission. There are still other questions that need to be addressed: How frequently should patients be screened? Which individuals should be tested? From where on the body should samples be collected? Will increased resistance develop from the decolonization procedures?

Even if identification and decolonization procedures are perfected, ethical questions will remain. Should patients have the right to decline testing? Should a patient who tests positive for MRSA have the right to decline the decolonization procedure, and if so, should hospitals have the right to refuse treatment to the patient? How do we balance the individual's right to receive care with the rights of other patients who could be exposed to disease as a result?

## Superficial Staphylococcal Infections

*S. aureus* is often associated with pyoderma, skin infections that are purulent. Pus formation occurs because many strains of *S. aureus* produce leukocidins, which kill white blood cells. These purulent skin infections may initially manifest as folliculitis, but can lead to furuncles or deeper abscesses called carbuncles.

Folliculitis generally presents as bumps and pimples that may be itchy, red, and/or pus-filled. In some cases, folliculitis is self-limiting, but if it continues for more than a few days, worsens, or returns repeatedly, it may require medical treatment. Sweat, skin injuries, ingrown hairs, tight clothing, irritation from shaving, and skin conditions can all contribute to folliculitis. Avoidance of tight clothing and skin irritation can help to prevent infection, but topical antibiotics (and sometimes other treatments) may also help. Folliculitis can be identified by skin inspection; treatment is generally started without first culturing and identifying the causative agent.

In contrast, furuncles (boils) are deeper infections (Figure 18.1.2). They are most common in those individuals (especially young adults and teenagers) who play contact sports, share athletic equipment, have poor nutrition, live in close quarters, or have weakened immune systems. Good hygiene and skin care can often help to prevent furuncles from becoming more infective, and they generally resolve on their own. However, if furuncles spread, increase in number or size, or lead to systemic symptoms such as fever and chills, then medical care is needed. They may sometimes need to be drained (at which time the pathogens can be cultured) and treated with antibiotics.

When multiple boils develop into a deeper lesion, it is called a carbuncle (Figure 18.1.2). Because carbuncles are deeper, they are more commonly associated with systemic symptoms and a general feeling of illness. Larger, recurrent, or worsening carbuncles require medical treatment, as do those associated with signs of illness such as fever. Carbuncles generally need to be drained and treated with antibiotics. While carbuncles are relatively easy to identify visually, culturing and laboratory analysis of the wound may be recommended for some infections because antibiotic resistance is relatively common.

Proper hygiene is important to prevent these types of skin infections or to prevent the progression of existing infections.




Figure 18.1.2: Furuncles (boils) and carbuncles are infections of the skin often caused by *Staphylococcus* bacteria. (a) A furuncle contains pus and exhibits swelling. (b) A carbuncle is a pus-filled lesion that is typically deeper than the furuncle. It often forms from multiple furuncles. (credit a: modification of work by "Mahdouch"/Wikimedia Commons; credit b: modification of work by "Drvgaikwad"/Wikimedia Commons)

Staphylococcal scalded skin syndrome (SSSS) is another superficial infection caused by *S. aureus* that is most commonly seen in young children, especially infants. Bacterial exotoxins first produce erythema (redness of the skin) and then severe peeling of the skin, as might occur after scalding (Figure 18.1.3). SSSS is diagnosed by examining characteristics of the skin (which may rub off easily), using blood tests to check for elevated white blood cell counts, culturing, and other methods. Intravenous antibiotics and fluid therapy are used as treatment.



Figure 18.1.3: A newborn with staphylococcal scalded skin syndrome (SSSS), which results in large regions of peeling, dead skin. (credit: modification of work by D Jeyakumari, R Gopal, M Eswaran, and C MaheshKumar)

## Key Concepts and Summary

- *Staphylococcus* causes many different types of skin infections, many of which occur when bacteria breach the skin barrier through a cut or wound.
- *S. aureus* are frequently associated with purulent skin infections that manifest as **folliculitis**, **furuncles**, or **carbuncles**. *S. aureus* is also a leading cause of staphylococcal scalded skin syndrome (SSSS).
- *S. aureus* is generally drug resistant and current MRSA strains are resistant to a wide range of antibiotics.
- Community-acquired and hospital-acquired staphyloccocal infections are an ongoing problem because many people are asymptomatic carriers.

## Footnotes


1. Starr, C.R. and Engelberg N.C. “Role of Hyaluronidase in Subcutaneous Spread and Growth of Group A Streptococcus.” *Infection and Immunity* 2006(7:1): 40–48. doi: 10.1128/IAI.74.1.40-48.2006.
2. Nuwayhid, Z.B., Aronoff, D.M., and Mulla, Z.D.. “Blunt Trauma as a Risk Factor for Group A Streptococcal Necrotizing Fasciitis.” *Annals of Epidemiology* (2007) 17:878–881.
3. Shadomy, S.V., Traxler, R.M., and Marston, C.K. “Infectious Diseases Related to Travel: Anthrax” 2015. Centers for Disease Control and Prevention. wwwnc.cdc.gov/travel/yellowbo...travel/anthrax. Accessed Sept 14, 2016.
4. US FDA. “Anthrax.” 2015. www.fda.gov/BiologicsBloodVac.../ucm061751.htm. Accessed Sept 14, 2016.
5. Berger, T., Kassirer, M., and Aran, A.A.. “Injectional Anthrax—New Presentation of an Old Disease.” *Euro Surveillance* 19 (2014) 32. http://www.ncbi.nlm.nih.gov/pubmed/25139073. Accessed Sept 14, 2016.
6. United Nations Office at Geneva. “What Are Biological and Toxin Weapons?” http://www.unog.ch/80256EE600585943/...2571860035A6DB?. Accessed Sept 14, 2016.
7. Federal Bureau of Investigation. “Famous Cases and Criminals: Amerithrax or Anthrax Investigation.” www.fbi.gov/history/famous-c...-investigation. Accessed Sept 14, 2016.
8. Centers for Disease Control and Prevention. “Anthrax: Medical Care: Prevention: Antibiotics.” www.cdc.gov/anthrax/medical-c...revention.html. Accessed Sept 14, 2016.
9. Emergent Biosolutions. AVA (BioThrax) vaccine package insert (Draft). Nov 2015. www.fda.gov/downloads/biologi...ductsblas/ucm0


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# 18.2: Review Questions

## Multiple Choice

1. *Staphylococcus aureus* is most often associated with being
   A. coagulase-positive.
   B. coagulase-negative.
   C. catalase-negative.
   D. gram-negative

*Answer available at the end of this section.*

## Fill in the Blank

2. A purulent wound produces _____.

*Answer available at the end of this section.*

## Short Answer

3. How are leukocidins associated with pus production?
4. What is a good first test to distinguish streptococcal infections from staphylococcal infections?

## Answers

**Multiple Choice**

A

**Fill in the Blank**

pus

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# 19.1: Bacterial Infections of the Reproductive System

**Learning Objectives**

- Identify the most common bacterial pathogens that can cause infections of the reproductive system
- Compare the major characteristics of specific bacterial diseases affecting the reproductive system

In addition to infections of the urinary tract, bacteria commonly infect the reproductive tract. As with the urinary tract, parts of the reproductive system closest to the external environment are the most likely sites of infection. Often, the same microbes are capable of causing urinary tract and reproductive tract infections.

## Gonorrhea

Also known as the clap, gonorrhea is a common sexually transmitted disease of the reproductive system that is especially prevalent in individuals between the ages of 15 and 24. It is caused by *Neisseria gonorrhoeae*, often called gonococcus or GC, which have fimbriae that allow the cells to attach to epithelial cells. It also has a type of lipopolysaccharide endotoxin called lipooligosaccharide as part of the outer membrane structure that enhances its pathogenicity. In addition to causing urethritis, *N. gonorrhoeae* can infect other body tissues such as the skin, meninges, pharynx, and conjunctiva.

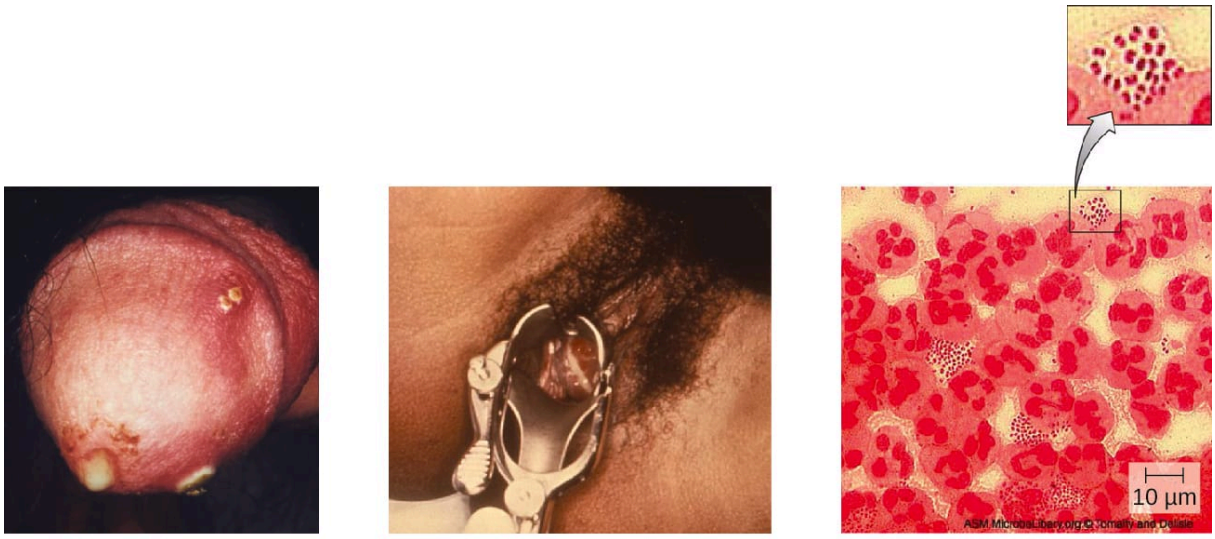



Figure 19.1.2: (a) Clinical photograph of gonococcal discharge from penis. The lesions on the skin could indicate co-infection with another STI. (b) Purulent discharge originating from the cervix and accumulating in the vagina of a patient with gonorrhea. (c) A micrograph of urethral discharge shows gram-negative diplococci (paired cells) both inside and outside the leukocytes (large cells with lobed nuclei). These results could be used to diagnose gonorrhea in a male patient, but female vaginal samples may contain other *Neisseria* spp. even if the patient is not infected with *N. gonorrhoeae*. (credit a, b: modification of work by Centers for Disease Control and Prevention; credit c: modification of work by American Society for Microbiology)

Many infected individuals (both men and women) are asymptomatic carriers of gonorrhea. When symptoms do occur, they manifest differently in males and females. Males may develop pain and burning during urination and discharge from the penis that may be yellow, green, or white (Figure 19.1.2). Less commonly, the testicles may become swollen or tender. Over time, these symptoms can increase and spread. In some cases, chronic infection develops. The disease can also develop in the rectum, causing symptoms such as discharge, soreness, bleeding, itching, and pain (especially in association with bowel movements).

Women may develop pelvic pain, discharge from the vagina, intermenstrual bleeding (i.e., bleeding not associated with normal menstruation), and pain or irritation associated with urination. As with men, the infection can become chronic. In women, however, chronic infection can cause increases in menstrual flow. Rectal infection can also occur, with the symptoms previously

described for men. Infections that spread to the endometrium and fallopian tubes can cause pelvic inflammatory disease (PID), characterized by pain in the lower abdominal region, dysuria, vaginal discharge, and fever. PID can also lead to infertility through scarring and blockage of the fallopian tubes (salpingitis); it may also increase the risk of a life-threatening ectopic pregnancy, which occurs when a fertilized egg begins developing somewhere other than the uterus (e.g., in the fallopian tube or ovary).

When a gonorrhea infection disseminates throughout the body, serious complications can develop. The infection may spread through the blood (bacteremia) and affect organs throughout the body, including the heart (gonorrheal endocarditis), joints (gonorrheal arthritis), and meninges encasing the brain (meningitis).

Urethritis caused by *N. gonorrhoeae* can be difficult to treat due to antibiotic resistance (see Micro Connections below). Some strains have developed resistance to the fluoroquinolones, so cephalosporins are often a first choice for treatment. Because co-infection with *C. trachomatis* is common, the CDC recommends treating with a combination regimen of ceftriaxone and azithromycin. Treatment of sexual partners is also recommended to avoid reinfection and spread of infection to others.[1]

### Exercise 19.1.2

1. What are some of the serious consequences of a gonorrhea infection?
2. What organism commonly coinfects with *N. gonorrhoeae*?

### Micro Connections

**Antibiotic Resistance in *Neisseria***

Antibiotic resistance in many pathogens is steadily increasing, causing serious concern throughout the public health community. Increased resistance has been especially notable in some species, such as *Neisseria gonorrhoeae*. The CDC monitors the spread of antibiotic resistance in *N. gonorrhoeae*, which it classifies as an urgent threat, and makes recommendations for treatment. So far, *N. gonorrhoeae* has shown resistance to cefixime (a cephalosporin), ceftriaxone (another cephalosporin), azithromycin, and tetracycline. Resistance to tetracycline is the most common, and was seen in 188,600 cases of gonorrhea in 2011 (out of a total 820,000 cases). In 2011, some 246,000 cases of gonorrhea involved strains of *N. gonorrhoeae* that were resistant to at least one antibiotic.[2] These resistance genes are spread by plasmids, and a single bacterium may be resistant to multiple antibiotics. The CDC currently recommends treatment with two medications, ceftriaxone and azithromycin, to attempt to slow the spread of resistance. If resistance to cephalosporins increases, it will be extremely difficult to control the spread of *N. gonorrhoeae*.

## Key Concepts and Summary

- **Gonorrhea** is caused by *N. gonorrhoeae*, which can cause infection of the reproductive and urinary tracts and is associated with symptoms of urethritis. If left untreated, it can progress to epididymitis, salpingitis, and pelvic inflammatory disease and enter the bloodstream to infect other sites in the body.

## Footnotes

1. Centers for Disease Control and Prevention. “2015 Sexually Transmitted Diseases Treatment Guidelines: Gonococcal Infections,” 2015. http://www.cdc.gov/std/tg2015/gonorrhea.htm.
2. Centers for Disease Control and Prevention. “Antibiotic Resistance Threats in the United States, 2013,” 2013. http://www.cdc.gov/drugresistance/pd...s-2013-508.pdf.
3. Centers for Disease Control and Prevention. “2015 Sexually Transmitted Diseases Treatment Guidelines: Chancroid,” 2015. http://www.cdc.gov/std/tg2015/chancroid.htm.
4. Ibid.
5. Centers for Disease Control and Prevention. “2014 Sexually Transmitted Disease Surveillance,” 2015. http://www.cdc.gov/std/stats14/default.htm.

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# 19.2: Review Questions

## Critical Thinking

1. Why does the CDC recommend a two-drug treatment regimen to cover both *C. trachomatis* and *N. gonorrhoeae* if testing to distinguish between the two is not available? Additionally, how does the two-drug treatment regimen address antibiotic resistance?

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# 20.1: Bacterial Infections of the Circulatory and Lymphatic Systems

**Learning Objectives**

- Identify and compare bacteria that most commonly cause infections of the circulatory and lymphatic systems
- Compare the major characteristics of specific bacterial diseases affecting the circulatory and lymphatic systems

Bacteria can enter the circulatory and lymphatic systems through acute infections or breaches of the skin barrier or mucosa. Breaches may occur through fairly common occurrences, such as insect bites or small wounds. Even the act of tooth brushing, which can cause small ruptures in the gums, may introduce bacteria into the circulatory system. In most cases, the bacteremia that results from such common exposures is transient and remains below the threshold of detection. In severe cases, bacteremia can lead to septicemia with dangerous complications such as toxemia, sepsis, and septic shock. In these situations, it is often the immune response to the infection that results in the clinical signs and symptoms rather than the microbes themselves.

## Bacterial Sepsis, Septic and Toxic Shock

At low concentrations, pro-inflammatory cytokines such as interleukin 1 (IL-1) and tumor necrosis factor-α (TNF-α) play important roles in the host's immune defenses. When they circulate systemically in larger amounts, however, the resulting immune response can be life threatening. IL-1 induces vasodilation (widening of blood vessels) and reduces the tight junctions between vascular endothelial cells, leading to widespread edema. As fluids move out of circulation into tissues, blood pressure begins to drop. If left unchecked, the blood pressure can fall below the level necessary to maintain proper kidney and respiratory functions, a condition known as septic shock. In addition, the excessive release of cytokines during the inflammatory response can lead to the formation of blood clots. The loss of blood pressure and occurrence of blood clots can result in multiple organ failure and death.

Bacteria are the most common pathogens associated with the development of sepsis, and septic shock.[1] The most common infection associated with sepsis is bacterial pneumonia (see Bacterial Infections of the Respiratory Tract), accounting for about half of all cases, followed by intra-abdominal infections (Bacterial Infections of the Gastrointestinal Tract) and urinary tract infections (Bacterial Infections of the Urinary System).[2] Infections associated with superficial wounds, animal bites, and indwelling catheters may also lead to sepsis and septic shock.

These initially minor, localized infections can be caused by a wide range of different bacteria, including *Staphylococcus, Streptococcus*, *Pseudomonas*, *Pasteurella, Acinetobacter,* and members of the Enterobacteriaceae. However, if left untreated, infections by these gram-positive and gram-negative pathogens can potentially progress to sepsis, shock, and death.

### Toxic Shock Syndrome and Streptococcal Toxic Shock-Like Syndrome

Toxemia associated with infections caused by *Staphylococcus aureus* can cause staphylococcal toxic shock syndrome (TSS). Some strains of *S. aureus* produce a superantigen called toxic shock syndrome toxin-1 (TSST-1). TSS may occur as a complication of other localized or systemic infections such as pneumonia, osteomyelitis, sinusitis, and skin wounds (surgical, traumatic, or burns). Those at highest risk for staphylococcal TSS are women with preexisting *S. aureus* colonization of the vagina who leave tampons, contraceptive sponges, diaphragms, or other devices in the vagina for longer than the recommended time.

Staphylococcal TSS is characterized by sudden onset of vomiting, diarrhea, myalgia, body temperature higher than 38.9 °C (102.0 °F), and rapid-onset hypotension with a systolic blood pressure less than 90 mm Hg for adults; a diffuse erythematous rash that leads to peeling and shedding skin 1 to 2 weeks after onset; and additional involvement of three or more organ systems.[3] The mortality rate associated with staphylococcal TSS is less than 3% of cases.

Diagnosis of staphylococcal TSS is based on clinical signs, symptoms, serologic tests to confirm bacterial species, and the detection of toxin production from staphylococcal isolates. Cultures of skin and blood are often negative; less than 5% are

positive in cases of staphylococcal TSS. Treatment for staphylococcal TSS includes decontamination, debridement, vasopressors to elevate blood pressure, and antibiotic therapy with clindamycin plus vancomycin or daptomycin pending susceptibility results.

A syndrome with signs and symptoms similar to staphylococcal TSS can be caused by *Streptococcus pyogenes*. This condition, called streptococcal toxic shock-like syndrome (STSS), is characterized by more severe pathophysiology than staphylococcal TSS,[4] with about 50% of patients developing *S. pyogenes* bacteremia and necrotizing fasciitis. In contrast to staphylococcal TSS, STSS is more likely to cause acute respiratory distress syndrome (ARDS), a rapidly progressive disease characterized by fluid accumulation in the lungs that inhibits breathing and causes hypoxemia (low oxygen levels in the blood). STSS is associated with a higher mortality rate (20%–60%), even with aggressive therapy. STSS usually develops in patients with a streptococcal soft-tissue infection such as bacterial cellulitis, necrotizing fasciitis, pyomyositis (pus formation in muscle caused by infection), a recent influenza A infection, or chickenpox.

**Exercise 20.1.1**

How can large amounts of pro-inflammatory cytokines lead to septic shock?

**Clinical Focus**

**Part 2**

Despite oxacillin therapy, Barbara's condition continued to worsen over the next several days. Her fever increased to 40.1 °C (104.2 °F) and she began to experience chills, rapid breathing, and confusion. Her doctor suspected bacteremia by a drug-resistant bacterium and admitted Barbara to the hospital. Cultures of the surgical site and blood revealed *Staphylococcus aureus*. Antibiotic susceptibility testing confirmed that the isolate was methicillin-resistant *S. aureus* (MRSA). In response, Barbara's doctor changed her antibiotic therapy to vancomycin and arranged to have the port and venous catheter removed.

- Why did Barbara's infection not respond to oxacillin therapy?
- Why did the physician have the port and catheter removed?
- Based on the signs and symptoms described, what are some possible diagnoses for Barbara's condition?

Jump to the next Clinical Focus feature box. Go back to the previous Clinical Focus feature box.

## Puerperal Sepsis

A type of sepsis called puerperal sepsis, also known as puerperal infection, puerperal fever, or childbed fever, is a nosocomial infection associated with the period of puerperium—the time following childbirth during which the mother's reproductive system returns to a nonpregnant state. Such infections may originate in the genital tract, breast, urinary tract, or a surgical wound. Initially the infection may be limited to the uterus or other local site of infection, but it can quickly spread, resulting in peritonitis, septicemia, and death. Before the 19th century work of Ignaz Semmelweis and the widespread acceptance of germ theory (see Modern Foundations of Cell Theory), puerperal sepsis was a major cause of mortality among new mothers in the first few days following childbirth.

Puerperal sepsis is often associated with *Streptococcus pyogenes*, but numerous other bacteria can also be responsible. Examples include gram-positive bacterial (e.g. *Streptococcus* spp., *Staphylococcus* spp., and *Enterococcus* spp.), gram-negative bacteria (e.g. *Chlamydia* spp., *Escherichia coli*, *Klebsiella* spp., and *Proteus* spp.), as well as anaerobes such as *Peptostreptococcus* spp., *Bacteroides* spp., and *Clostridium* spp. In cases caused by *S. pyogenes*, the bacteria attach to host tissues using M protein and produce a carbohydrate capsule to avoid phagocytosis. *S. pyogenes* also produces a variety of exotoxins, like streptococcal pyrogenic exotoxins A and B, that are associated with virulence and may function as superantigens.

Diagnosis of puerperal fever is based on the timing and extent of fever and isolation, and identification of the etiologic agent in blood, wound, or urine specimens. Because there are numerous possible causes, antimicrobial susceptibility testing must be used to determine the best antibiotic for treatment. Nosocomial incidence of puerperal fever can be greatly reduced through the use of antiseptics during delivery and strict adherence to handwashing protocols by doctors, midwives, and nurses.

## Infectious Arthritis

Also called septic arthritis, infectious arthritis can be either an acute or a chronic condition. Infectious arthritis is characterized by inflammation of joint tissues and is most often caused by bacterial pathogens. Most cases of acute infectious arthritis are secondary to bacteremia, with a rapid onset of moderate to severe joint pain and swelling that limits the motion of the affected joint. In adults and young children, the infective pathogen is most often introduced directly through injury, such as a wound or a surgical site, and brought to the joint through the circulatory system. Acute infections may also occur after joint replacement surgery. Acute infectious arthritis often occurs in patients with an immune system impaired by other viral and bacterial infections. *S. aureus* is the most common cause of acute septic arthritis in the general population of adults and young children. *Neisseria gonorrhoeae* is an important cause of acute infectious arthritis in sexually active individuals.

Chronic infectious arthritis is responsible for 5% of all infectious arthritis cases and is more likely to occur in patients with other illnesses or conditions. Patients at risk include those who have an HIV infection, a bacterial or fungal infection, prosthetic joints, rheumatoid arthritis (RA), or who are undergoing immunosuppressive chemotherapy. Onset is often in a single joint; there may be little or no pain, aching pain that may be mild, gradual swelling, mild warmth, and minimal or no redness of the joint area.

Diagnosis of infectious arthritis requires the aspiration of a small quantity of synovial fluid from the afflicted joint. Direct microscopic evaluation, culture, antimicrobial susceptibility testing, and polymerase chain reaction (PCR) analyses of the synovial fluid are used to identify the potential pathogen. Typical treatment includes administration of appropriate antimicrobial drugs based on antimicrobial susceptibility testing. For nondrug-resistant bacterial strains, β-lactams such as oxacillin and cefazolin are often prescribed for staphylococcal infections. Third-generation cephalosporins (e.g., ceftriaxone) are used for increasingly prevalent β-lactam-resistant *Neisseria* infections. Infections by *Mycobacterium* spp. or fungi are treated with appropriate long-term antimicrobial therapy. Even with treatment, the prognosis is often poor for those infected. About 40% of patients with nongonnococcal infectious arthritis will suffer permanent joint damage and mortality rates range from 5% to 20%.[5] Mortality rates are higher among the elderly.[6]

## Osteomyelitis

Osteomyelitis is an inflammation of bone tissues most commonly caused by infection. These infections can either be acute or chronic and can involve a variety of different bacteria. The most common causative agent of osteomyelitis is *S. aureus*. However, *M. tuberculosis*, *Pseudomonas aeruginosa, Streptococcus pyogenes*, *S. agalactiae*, species in the Enterobacteriaceae, and other microorganisms can also cause osteomyelitis, depending on which bones are involved. In adults, bacteria usually gain direct access to the bone tissues through trauma or a surgical procedure involving prosthetic joints. In children, the bacteria are often introduced from the bloodstream, possibly spreading from focal infections. The long bones, such as the femur, are more commonly affected in children because of the more extensive vascularization of bones in the young.[7]

The signs and symptoms of osteomyelitis include fever, localized pain, swelling due to edema, and ulcers in soft tissues near the site of infection. The resulting inflammation can lead to tissue damage and bone loss. In addition, the infection may spread to joints, resulting in infectious arthritis, or disseminate into the blood, resulting in sepsis and thrombosis(formation of blood clots). Like septic arthritis, osteomyelitis is usually diagnosed using a combination of radiography, imaging, and identification of bacteria from blood cultures, or from bone cultures if blood cultures are negative. Parenteral antibiotic therapy is typically used to treat osteomyelitis. Because of the number of different possible etiologic agents, however, a variety of drugs might be used. Broad-spectrum antibacterial drugs such as nafcillin, oxacillin, or cephalosporin are typically prescribed for acute osteomyelitis, and ampicillin and piperacillin/tazobactam for chronic osteomyelitis. In cases of antibiotic resistance, vancomycin treatment is sometimes required to control the infection. In serious cases, surgery to remove the site of infection may be required. Other forms of treatment include hyperbaric oxygen therapy (see Using Physical Methods to Control Microorganisms) and implantation of antibiotic beads or pumps.

**Exercise 20.1.2**

What bacterium the most common cause of both septic arthritis and osteomyelitis?

## Key Concepts and Summary

- Bacterial infections of the circulatory system are almost universally serious. Left untreated, most have high mortality rates.
- Bacterial pathogens usually require a breach in the immune defenses to colonize the circulatory system. Most often, this involves a wound or the bite of an arthropod vector, but it can also occur in hospital settings and result in nosocomial infections.
- **Sepsis** from both gram-negative and gram-positive bacteria, **puerperal fever, osteomyelitis,** and **toxic shock syndrome** are typically a result of injury or introduction of bacteria by medical or surgical intervention.
- Because their symptoms are so similar to those of other diseases, many bacterial infections of the circulatory system are difficult to diagnose.
- Standard antibiotic therapies are effective for the treatment of most bacterial infections of the circulatory system, unless the bacterium is resistant, in which case synergistic treatment may be required.
- The systemic immune response to a bacteremia, which involves the release of excessive amounts of cytokines, can sometimes be more damaging to the host than the infection itself.

## Footnotes


1. S.P. LaRosa. “Sepsis.” 2010. http://www.clevelandclinicmeded.com/...isease/sepsis/.
2. D.C. Angus, T. Van der Poll. “Severe Sepsis and Septic Shock.” *New England Journal of Medicine* 369, no. 9 (2013):840–851.
3. Centers for Disease Control and Prevention. “Toxic Shock Syndrome (Other Than Streptococcal) (TSS) 2011 Case Definition.” https://wwwn.cdc.gov/nndss/condition...finition/2011/. Accessed July 25, 2016.
4. Centers for Disease Control and Prevention. “Streptococcal Toxic Shock Syndrome (STSS) (*Streptococcus pyogenes*) 2010 Case Definition.” https://wwwn.cdc.gov/nndss/condition...finition/2010/. Accessed July 25, 2016.
5. M.E. Shirtliff, Mader JT. “Acute Septic Arthritis.” *Clinical Microbiology Reviews* 15 no. 4 (2002):527–544.
6. J.R. Maneiro et al. “Predictors of Treatment Failure and Mortality in Native Septic Arthritis.” *Clinical Rheumatology* 34, no. 11 (2015):1961–1967.
7. M. Vazquez. “Osteomyelitis in Children.” *Current Opinion in Pediatrics* 14, no. 1 (2002):112–115.
8. A. Beaudoin et al. “Acute Rheumatic Fever and Rheumatic Heart Disease Among Children—American Samoa, 2011–2012.” *Morbidity and Mortality Weekly Report* 64 no. 20 (2015):555–558.
9. M.A. Gerber et al. “Prevention of Rheumatic Fever and Diagnosis and Treatment of Acute Streptococcal Pharyngitis: A Scientific Statement From the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Young, the Interdisciplinary Council on Functional Genomics and Translational Biology, and the Interdisciplinary Council on Quality of Care and Outcomes Research: Endorsed by the American Academy of Pediatrics.” *Circulation* 119, no. 11 (2009):1541–1551.
10. World Health Organization. “WHO Guidelines on Tularaemia.” 2007. http://www.cdc.gov/tularemia/resources/whotularemiamanual.pdf. Accessed July 26, 2016.
11. MOH Key Laboratory of Systems Biology of Pathogens. “Virulence Factors of Pathogenic Bacteria, *Yersinia*.” http://www.mgc.ac.cn/cgi-bin/VFs/gen...Genus=Yersinia. Accessed September 9, 2016.
12. Rosen, William. Justinian’s Flea: Plague, Empire, and the Birth of Europe. Viking Adult; pg 3; ISBN 978-0-670-03855-8.
13. Benedictow, Ole J. 2004. The Black Death 1346-1353: The Complete History. Woodbridge: Boydell Press.
14. Centers for Disease Control and Prevention. “Plague: History.” http://www.cdc.gov/plague/history/. Accessed September 15, 2016.
15. J.S. Bakken et al. “Diagnosis and Management of Tickborne Rickettsial Diseases: Rocky Mountain Spotted Fever, Ehrlichioses, and Anaplasmosis–United States. A Practical Guide for Physicians and Other Health Care and Public Health Professionals.” *MMWR Recommendations and Reports* 55 no. RR04 (2006):1–27.
16. MOH Key Laboratory of Systems Biology of Pathogens, “Virulence Factors of Pathogenic Bacteria, Anaplasma” 2016. http://www.mgc.ac.cn/cgi-bin/VFs/jsif/main.cgi. Accessed July, 26, 2016.
17. Centers for Disease Control and Prevention. “Ehrlichiosis, Symptoms, Diagnosis, and Treatment.” 2016. https://www.cdc.gov/ehrlichiosis/symptoms/index.html. Accessed July 29, 2016.
18. Drali, R., Brouqui, P. and Raoult, D. “Typhus in World War I.” *Microbiology Today* 41 (2014) 2:58–61.
19. Centers for Disease Control and Prevention. *CDC Health Information for International Travel 2014: The Yellow Book*. Oxford University Press, 2013. http://wwwnc.cdc.gov/travel/yellowbook/2016/infectious-diseases-related-to-travel/rickettsial-spotted-typhus-fevers-related-infections-anaplasmosis-ehrlichiosis. Accessed July 26, 2016.
20. World Health Organization. “Typhus.” 1997. www.who.int/mediacentre/factsheets/fs162/en/. Accessed July 26, 2016.
21. Centers for Disease Control and Prevention. “Rocky Mountain Spotted Fever (RMSF): Statistics and Epidemiology.” http://www.cdc.gov/rmsf/stats/index.html. Accessed Sept 16, 2016.
22. Centers for Disease Control and Prevention. “Lyme Disease. Data and Statistics.” 2015. http://www.cdc.gov/lyme/stats/

index.html. Accessed July 26, 2016.
23. Centers for Disease Control and Prevention. “Signs and Symptoms of Untreated Lyme Disease.” 2015. http://www.cdc.gov/lyme/signs_symptoms/index.html. Accessed July 27, 2016.
24. Centers for Disease Control and Prevention. “Ticks. Symptoms of Tickborne Illness.” 2015. http://www.cdc.gov/ticks/symptoms.html. Accessed July 27, 2016.

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# 20.2: Viral Infections of the Circulatory and Lymphatic Systems

**Learning Objectives**

- Identify common viral pathogens that cause infections of the circulatory and lymphatic systems
- Compare the major characteristics of specific viral diseases affecting the circulatory and lymphatic systems

Viral pathogens of the circulatory system vary tremendously both in their virulence and distribution worldwide. Some of these pathogens are practically global in their distribution. Fortunately, the most ubiquitous viruses tend to produce the mildest forms of disease. In the majority of cases, those infected remain asymptomatic. On the other hand, other viruses are associated with life-threatening diseases that have impacted human history.

## Human Immunodeficiency Virus

Human T-lymphotropic viruses (HTLV), also called human immunodeficiency viruses (HIV) are retroviruses that are the causative agent of acquired immune deficiency syndrome (AIDS). There are two main variants of human immunodeficiency virus (HIV). HIV-1 (Figure 20.2.4) occurs in human populations worldwide, whereas HIV-2 is concentrated in West Africa. Currently, the most affected region in the world is sub-Saharan Africa, with an estimated 25.6 million people living with HIV in 2015.[15] Sub-Saharan Africa also accounts for two-thirds of the global total of new HIV infections (Figure 20.2.5).[16]

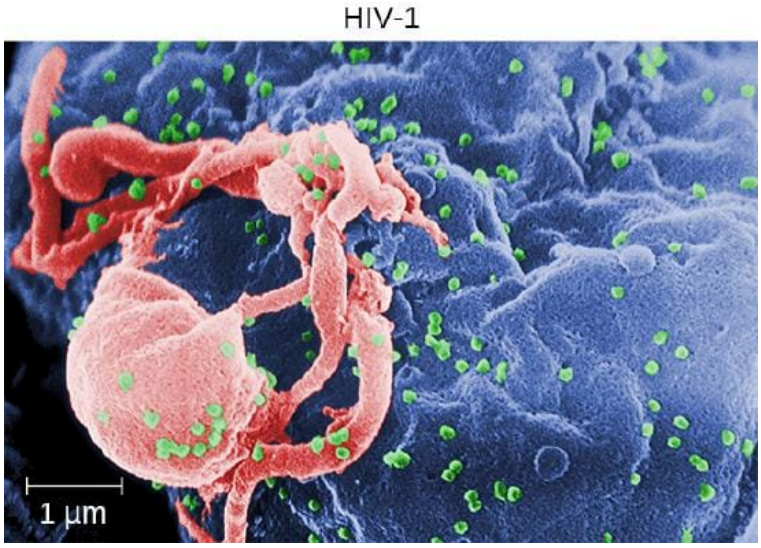



Figure 20.2.4: This micrograph shows HIV particles (green) budding from a lymphocyte (top right). (credit: modification of work by Centers for Disease Control and Prevention)

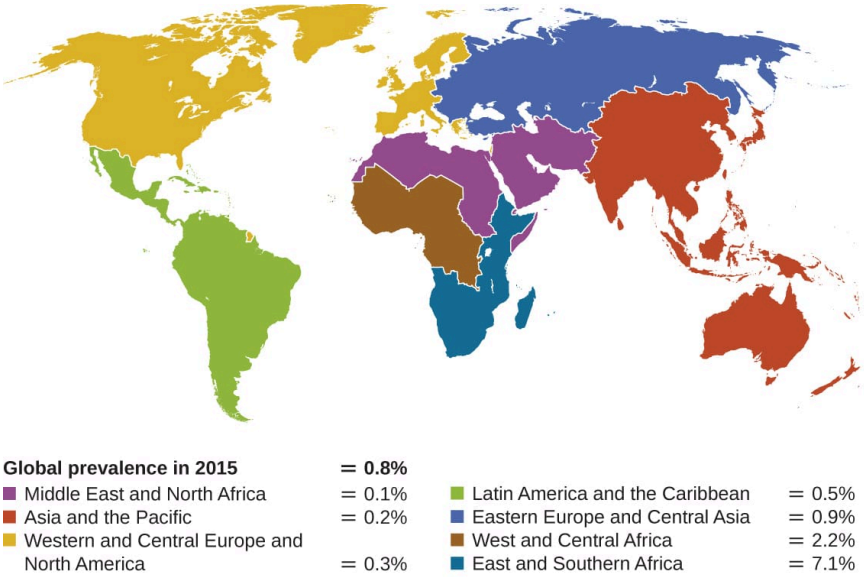



Figure 20.2.5: This map shows the prevalence of HIV worldwide in 2015 among adults ages 15–49 years.

HIV is spread through direct contact with body fluids. Casual contact and insect vectors are not sufficient for disease transmission; common modes of transmission include sexual contact and sharing of needles by intravenous (IV) drug users. It generally takes many years before the effects of an HIV infection are detected. HIV infections are not dormant during this period: virions are continually produced, and the immune system continually attempts to clear the viral infection, while the virus persistently infects additional CD4 T cells. Over time, the CD4 T-cell population is devastated, ultimately leading to AIDS.

When people are infected with HIV, their disease progresses through three stages based on CD4 T-cell counts and the presence of clinical symptoms (Figure 20.2.6).

- **Stage 1: Acute HIV infection.** Two to 4 weeks after infection with HIV, patients may experience a flu-like illness, which can last for a few weeks. Patients with acute HIV infection have more than 500 cells/μL CD4 T cells and a large amount of virus in their blood. Patients are very contagious during this stage. To confirm acute infection, either a fourth-generation antibody-antigen test or a nucleic acid test (NAT) must be performed.
- **Stage 2: Clinical latency.** During this period, HIV enters a period of dormancy. Patients have between 200 and 499 cells/μL CD4 T cells; HIV is still active but reproduces at low levels, and patients may not experience any symptoms of illness. For patients who are not taking medicine to treat HIV, this period can last a decade or longer. For patients receiving antiretroviral therapy, the stage may last for several decades, and those with low levels of the virus in their blood are much less likely to transmit HIV than those who are not virally suppressed. Near the end of the latent stage, the patient's viral load starts to increase and the CD4 T-cell count begins to decrease, leading to the development of symptoms and increased susceptibility to opportunistic infections.
- **Stage 3: Acquired immunodeficiency syndrome (AIDS).** Patients are diagnosed with AIDS when their CD4 T-cell count drops below 200 cells/μL or when they develop certain opportunistic illnesses. During this stage, the immune system becomes severely damaged by HIV. Common symptoms of AIDS include chills, fever, sweats, swollen lymph glands, weakness, and weight loss; in addition, patients often develop rare cancers such as Kaposi's sarcoma and opportunistic infections such as *Pneumocystis* pneumonia, tuberculosis, cryptosporidiosis, and toxoplasmosis. This is a fatal progression that, in the terminal stages, includes wasting syndrome and dementia complex. Patients with AIDS have a high viral load and are highly infectious; they typically survive about 3 years without treatment.

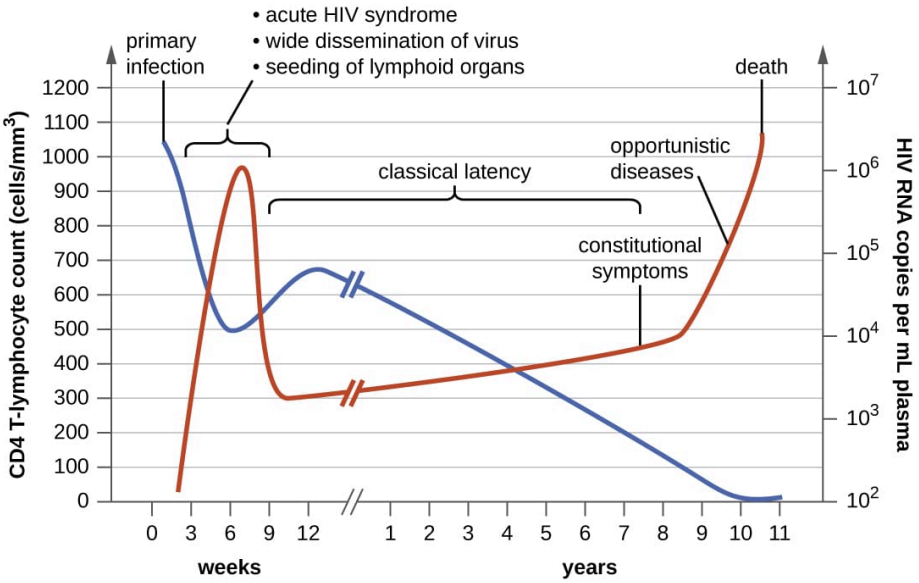



Figure 20.2.6: This graph shows the clinical progression of CD4 T cells (blue line), clinical symptoms, and viral RNA (red line) during an HIV infection. (credit: modification of work by Kogan M, and Rappaport J)

The initial diagnosis of HIV is performed using a serological test for antibody production against the pathogen. Positive test results are confirmed by Western blot or PCR tests. It can take weeks or months for the body to produce antibodies in response to an infection. There are fourth-generation tests that detect HIV antibodies and HIV antigens that are present even before the body begins producing antibodies. Nucleic acid tests (NATs) are a third type of test that is relatively expensive and uncommon; NAT can detect HIV in blood and determine the viral load.

As a consequence of provirus formation, it is currently not possible to eliminate HIV from an infected patient's body. Elimination by specific antibodies is ineffective because the virus mutates rapidly—a result of the error-prone reverse transcriptase and the inability to correct errors. Antiviral treatments, however, can greatly extend life expectancy. To combat the problem of drug resistance, combinations of antiretroviral drugs called antiretroviral therapy (ART), sometimes called highly active ART or combined ART, are used. There are several different targets for antiviral drug action (and a growing list of drugs for each of these targets). One class of drugs inhibits HIV entry; other classes inhibit reverse transcriptase by blocking viral RNA-dependent and DNA-dependent DNA polymerase activity; and still others inhibit one of the three HIV enzymes needed to replicate inside human cells.

## Exercise 20.2.5

Why is it not yet possible to cure HIV infections?

## Eye on Ethics

**HIV, AIDS, and Education**

When the first outbreaks of AIDS in the US occurred in the early 1980s, very little was known about the disease or its origins. Erroneously, the disease quickly became stigmatized as one associated with what became identified as at-risk behaviors such as sexual promiscuity, homosexuality, and IV drug use, even though mounting evidence indicated the disease was also contracted through transfusion of blood and blood products or by fetuses of infected mothers. In the mid-1980s, scientists elucidated the identity of the virus, its mode of transmission, and mechanisms of pathogenesis. Campaigns were undertaken to educate the public about how HIV spreads to stem infection rates and encourage behavioral changes that reduced the risk for infection. Approaches to this campaign, however, emphasized very different strategies. Some groups favored educational programs that emphasized sexual abstinence, monogamy, heterosexuality, and "just say no to drugs." Other groups placed an emphasis on "safe sex" in sex education programs and advocated social services programs that passed out free condoms to anyone, including sexually active minors, and provided needle exchange programs for IV drug users.

These are clear examples of the intersection between disease and cultural values. As a future health professional, what is your responsibility in terms of educating patients about behaviors that put them at risk for HIV or other diseases while possibly setting your own personal opinions aside? You will no doubt encounter patients whose cultural and moral values differ from your own. Is it ethical for you to promote your own moral agenda to your patients? How can you advocate for practical disease prevention while still respecting the personal views of your patients?

## Disease Profile

**Viral Diseases of the Circulatory and Lymphatic Systems**

Many viruses are able to cause systemic, difficult-to-treat infections because of their ability to replicate within the host. Some of the more common viruses that affect the circulatory system are summarized in Figure 20.2.7.

**Viral Diseases of the Circulatory and Lymphatic Systems**

| Disease | Pathogen | Signs and Symptoms | Transmission | Diagnostic Tests | Antimicrobial Drugs |
|---|---|---|---|---|---|
| AIDS/HIV infection | Human immunodeficiency virus (HIV) | Flu-like symptoms during acute stage, followed by long period of clinical latency; final stage (AIDS) includes fever, weight loss, wasting syndrome, dementia, and opportunistic secondary infections leading to death | Contact with body fluids (e.g., sexual contact, use of contaminated needles) | Serological tests for antibodies and/or HIV antigens; nucleic acid test (NAT) for presence of virus | Antiretroviral therapy (ART) using various combinations of drugs |
| Burkitt lymphoma | Epstein-Barr virus (human herpesvirus-4 [HHV-4]) | Rapid formation of malignant B-cell tumors, oral hairy leukoplakia; fatal if not promptly treated | Contact with body fluids (e.g., saliva, blood, semen); primarily affects patients immunocompromised by HIV or malaria | CT scans, tumor biopsy | Intensive alternating chemotherapy regimen |
| Chikungunya fever | Chikungunya virus | Fever, rash, joint pain | Transmitted between humans by *Aedes aegypti* and *A. albopictus* vectors | Viral culture, IFA, EIA, ELISA, PCR, RT-PCR | None |
| Cytomegalovirus infection | Cytomegalovirus (HHV-5) | Usually asymptomatic but may cause non-Epstein-Barr mononucleosis in adults; may cause developmental issues in developing fetus; in transplant recipients, may cause fever, transplant rejection, death | Contact with body fluids, blood transfusions, organ transplants; infected mothers can transmit virus to fetus transplacentally or to newborn in breastmilk, saliva | Histology, culture, EIA, IFA, PCR | Ganciclovir, valganciclovir, foscarnet, cidofovir |
| Dengue fever (breakbone fever) | Dengue fever viruses 1–4 | Fever, headache, extreme bone and joint pain, abdominal pain, vomiting, hemorrhaging; can be fatal | Transmitted between humans by *A. aegypti* and *A. albopictus* vectors | Serologic testing, ELISA, and PCR | None |
| Ebola virus disease (EVD) | Ebola virus | Fever, headache, joint pain, diarrhea, vomiting, hemorrhaging in gastrointestinal tract; organ failure; often fatal | Contact with body fluids (e.g., blood, saliva, sweat, urine, feces, vomit); highly contagious | ELISA, IgM ELISA, PCR, virus isolation | None |
| Hantavirus pulmonary syndrome (HPS) | Hantavirus | Initial flu-like symptoms followed by pulmonary edema and hypotension leading to pneumonia and shock; can be fatal | Inhalation of dried feces, urine from infected mouse or rat | ELISA, Western blot, RIBA, RT-PCR | None |
| Hemorrhagic fever with renal syndrome | Hantavirus | Fever, headache, nausea, rash, or eye inflammation, followed by hemorrhaging and kidney failure; can be fatal | Inhalation of dried feces, urine from infected mouse or rat | ELISA, Western blot, RIBA, RT-PCR | None |
| Infectious mononucleosis | Epstein-Barr virus (HHV-4), cytomegalovirus (HHV-5) | Pharyngitis, fever, extreme fatigue; swelling of lymph nodes, spleen, and liver | Contact with body fluids (e.g., saliva, blood, semen) | Tests for antibodies to various EBV-associated antigens | None |
| Yellow fever | Yellow fever virus | Dizziness, fever, chills, headache, myalgia, nausea, vomiting, constipation, fatigue; moderate to severe cases may include jaundice, rash, mucosal hemorrhaging, seizures, shock, and death | From monkeys to humans or between humans via *Aedes* or *Haemagogus* mosquito vectors | Culture, serology, PCR | None for treatment; preventive vaccine available |

Figure 20.2.7: Viral diseases of the Circulatory and Lymphatic systems.

## Key Concepts and Summary

- Patients infected with **human immunodeficiency virus (HIV)** progress through three stages of disease, culminating in **AIDS**. **Antiretroviral therapy (ART)** uses various combinations of drugs to suppress viral loads, extending the period of latency and reducing the likelihood of transmission.

## Footnotes


1. Centers for Disease Control and Prevention. “Cytomegalovirus (CMV) and Congenital CMV Infection: About CMV.” 2016. www.cdc.gov/cmv/transmission.html. Accessed July 28, 2016.
2. Centers for Disease Control and Prevention. “Cytomegalovirus (CMV) and Congenital CMV Infection: Babies Born with CMV (Congenital CMV Infection).” 2016. http://www.cdc.gov/cmv/congenital-infection.html. Accessed July 28, 2016.
3. ibid.
4. E. Cordero et al. “Cytomegalovirus Disease in Kidney Transplant Recipients: Incidence, Clinical Profile, and Risk Factors.” *Transplantation Proceedings* 44 no. 3 (2012):694–700.
5. L.M. Mofenson et al. “Guidelines for the Prevention and Treatment of Opportunistic Infections Among HIV-Exposed and HIV-Infected Children: Recommendations From CDC, the National Institutes of Health, the HIV Medicine Association of the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the American Academy of Pediatrics.” *MMWR Recommendations and Reports* 58 no. RR-11 (2009):1–166.
6. Centers for Disease Control and Prevention. “History Timeline Transcript.” http://www.cdc.gov/travel-training/local/HistoryEpidemiologyandVaccination/HistoryTimelineTranscript.pdf. Accessed July 28, 2016.

7. Centers for Disease Control and Prevention. “Yellow Fever, Symptoms and Treatment.” 2015 http://www.cdc.gov/yellowfever/symptoms/index.html. Accessed July 28, 2016.
8. J.T. Cathey, J.S. Marr. “Yellow fever, Asia and the East African Slave Trade.” *Transactions of the Royal Society of Tropical Medicine and Hygiene* 108, no. 5 (2014):252–257.
9. Centers for Disease Control and Prevention. “Dengue, Epidemiology.” 2014. http://www.cdc.gov/dengue/epidemiology/index.html. Accessed July 28, 2016.
10. C.R. Pringle “Dengue.” MSD Manual: Consumer Version. https://www.msdmanuals.com/home/infections/viral-infections/dengue. 2016. Accessed Sept 15, 2016.
11. HealthMap. “2014 Ebola Outbreaks.” http://www.healthmap.org/ebola/#timeline. Accessed July 28, 2016.
12. World Health Organization. “Hantavirus Diseases.” 2016. www.who.int/ith/diseases/hantavirus/en/. Accessed July 28, 2016.
13. ibid.
14. Centers for Disease Control and Prevention. “Hantavirus: Treatment.” 2012. http://www.cdc.gov/hantavirus/technical/hps/treatment.html. Accessed July 28, 2016.
15. World Health Organization. “HIV/AIDS: Fact Sheet.” 2016. http://www.who.int/mediacentre/factsheets/fs360/en/. Accessed July 28, 2016.
16. ibid.



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# 19: UROGENITAL SYSTEM INFECTIONS

The urogenital system is a combination of the urinary tract and reproductive system. Because both systems are open to the external environment, they are prone to infections. Some infections are introduced from outside, whereas others result from imbalances in the microbiota of the urogenital tract.

Urinary tract infections (UTIs) are one the most common bacterial infections worldwide, affecting over 100 million people each year. During 2007 in the United States, doctor office visits for UTIs exceeded 10 million, and an additional 2–3 million emergency department visits were attributed to UTIs. Sexually transmitted infections (STIs) also primarily affect the urogenital system and are an important cause of patient morbidity. The Centers for Disease Control and Prevention (CDC) estimates that there are approximately 20 million new cases of reportable STIs annually in the United States, half of which occur in people aged 15–24 years old. When STIs spread to the reproductive organs, they can be associated with severe morbidity and loss of fertility.

Because males and females have different urogenital anatomy, urogenital infections may affect males and females differently. In this chapter, we will discuss the various microbes that cause urogenital disease and the factors that contribute to their pathogenicity.

## Chapter Outline

19.1: Bacterial Infections of the Reproductive System

19.2: Review Questions

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# 20: CIRCULATORY AND LYMPHATIC SYSTEM INFECTIONS (PART D)

Yellow fever was once common in the southeastern US, with annual outbreaks of more than 25,000 infections in New Orleans in the mid-1800s.[1] In the early 20th century, efforts to eradicate the virus that causes yellow fever were successful thanks to vaccination programs and effective control (mainly through the insecticide dichlorodiphenyltrichloroethane [DDT]) of *Aedes aegypti*, the mosquito that serves as a vector. Today, the virus has been largely eradicated in North America.

Elsewhere, efforts to contain yellow fever have been less successful. Despite mass vaccination campaigns in some regions, the risk for yellow fever epidemics is rising in dense urban cities in Africa and South America.[2] In an increasingly globalized society, yellow fever could easily make a comeback in North America, where *A. aegypti* is still present. If these mosquitoes were exposed to infected individuals, new outbreaks would be possible.

Like yellow fever, many of the circulatory and lymphatic diseases discussed in this chapter are emerging or re-emerging worldwide. Despite medical advances, diseases like malaria, Ebola, and others could become endemic in the US given the right circumstances.

## Chapter Outline


20.1: Bacterial Infections of the Circulatory and Lymphatic Systems

20.2: Viral Infections of the Circulatory and Lymphatic Systems

20.3: Review Questions


## Footnotes

1. Centers for Disease Control and Prevention. “The History of Yellow Fever.” http://www.cdc.gov/travel-training/local/HistoryEpidemiologyandVaccination/page27568.html
2. C.L. Gardner, K.D. Ryman. “Yellow Fever: A Reemerging Threat.” *Clinical Laboratory Medicine* 30 no. 1 (2010):237–260.


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# 20.3: Review Questions

## Multiple Choice

1. A patient at a clinic has tested positive for HIV. Her blood contained 700/µL CD4 T cells and she does not have any apparent illness. Her infection is in which stage?
   A. 1
   B. 2
   C. 3

*Answer available at the end of this section.*

## Fill in the Blank

2. _____ refers to a loss of blood pressure resulting from a system-wide infection.

*Answer available at the end of this section.*

## Short Answer

3. Describe the progression of an HIV infection over time with regard to the number of circulating viruses, host antibodies, and CD4 T cells.
4. Describe the general types of diagnostic tests used to diagnose patients infected with HIV.
5. Identify the general categories of drugs used in ART used to treat patients infected with HIV.

## Answers

**Multiple Choice**

A

**Fill in the Blank**

Septic shock

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# A: Fundamentals of Physics and Chemistry Important to Microbiology

Like all other matter, the matter that comprises microorganisms is governed by the laws of chemistry and physics. The chemical and physical properties of microbial pathogens—both cellular and acellular—dictate their habitat, control their metabolic processes, and determine how they interact with the human body. This appendix provides a review of some of the fundamental principles of chemistry and physics that are essential to an understanding of microbiology. Many of the chapters in this text—especially Microbial Biochemistry and Microbial Metabolism—assume that the reader already has an understanding of the concepts reviewed here.

## Atomic Structure

Life is made up of matter. Matter occupies space and has mass. All matter is composed of **atoms**. All atoms contain **protons**, **electrons**, and **neutrons** (Figure $A.1$). The only exception is hydrogen (H), which is made of one proton and one electron. A proton is a positively charged particle that resides in the nucleus (the core of the atom) of an atom and has a mass of 1 atomic mass unit (amu) and a charge of +1. An electron is a negatively charged particle that travels in the space around the nucleus. Electrons are distributed in different energy levels called electron shells. Electrons have a negligible mass and a charge of –1. Neutrons, like protons, reside in the nucleus of an atom. They have a mass of 1 amu and no charge (neutral). The positive (proton) and negative (electron) charges balance each other in a neutral atom, which has a net zero charge. Because protons and neutrons each have a mass of 1 amu, the mass of an atom is equal to the number of protons and neutrons of that atom. The number of electrons does not factor into the overall mass because electron mass is so small.

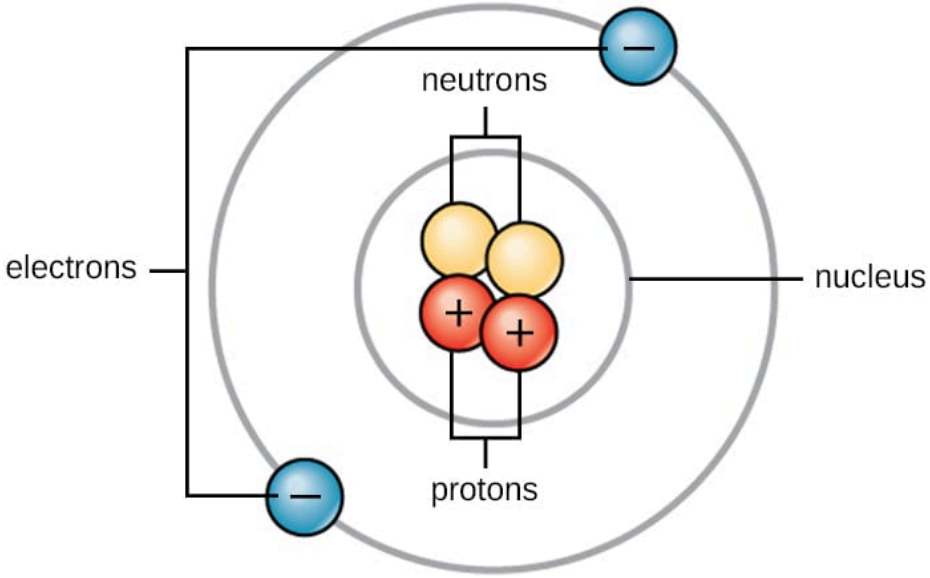



Figure $A.1$: Atoms are made up of protons and neutrons located within the nucleus and electrons surrounding the nucleus.

## Chemical Elements

All matter is composed of atoms of **elements**. Elements have unique physical and chemical properties and are substances that cannot easily be transformed either physically or chemically into other substances. Each element has been given a name, usually derived from Latin or English. The elements also have one- or two-letter symbols representing the name; for example, sodium (Na), gold (Au), and silver (Ag) have abbreviations derived from their original Latin names *natrium*, *aurum,* and *argentum*, respectively. Examples with English abbreviations are carbon (C), hydrogen (H), oxygen (O), and nitrogen (N). A total of 118 different elements (92 of which occur naturally) have been identified and organized into the periodic table of elements. Of the naturally occurring elements, fewer than 30 are found in organisms on Earth, and four of those (C, H, O, and N) make up approximately 96% of the mass of an organism.[1]

Each unique element is identified by the number of protons in its atomic nucleus. In addition to protons, each element's atomic nucleus contains an equal or greater number of neutrons (with the exception of hydrogen, which has only one proton). The total number of protons per element is described as the **atomic number**, and the combined mass of protons and neutrons is called the atomic mass or **mass number**. Therefore, it is possible to determine the number of neutrons by subtracting the atomic number from the mass number.

**Isotopes** are different forms of the same element that have the same number of protons, but a different number of neutrons. Many elements have several isotopes with one or two commonly occurring isotopes in nature. For example, carbon-12 ($^{12}C$), the most common isotope of carbon (98.6% of all C found on Earth),[2] contains six protons and six neutrons. Therefore, it has a mass number of 12 (6 protons + 6 neutrons) and an atomic number of 6.

There are two additional types of isotopes in nature: heavy isotopes, and radioisotopes. Heavy isotopes have one or more extra neutrons while still maintaining a stable atomic nucleus. An example of a heavy isotope is carbon-13 ($^{13}C$) (1.1% of all carbon).[3] $^{13}C$ has a mass number of 13 (6 protons + 7 neutrons). Since the atomic number of $^{13}C$ is 6, it is still the element carbon; however, it has more mass than the more common form of the element, $^{12}C$, because of the extra neutron in the nucleus. Carbon-14 ($^{14}C$) (0.0001% of all carbon)[4] is an example of a radioisotope. $^{14}C$ has a mass number of 14 (6 protons + 8 neutrons); however, the extra neutrons in $^{14}C$ result in an unstable nucleus. This instability leads to the process of radioactive decay. Radioactive decay involves the loss of one or more neutrons and the release of energy in the form of gamma rays, alpha particles, or beta particles (depending on the isotope).

Heavy isotopes and radioisotopes of carbon and other elements have proven to be useful in research, industry, and medicine.

# Chemical Bonds

There are three types of chemical bonds that are important when describing the interaction of atoms both within and between molecules in microbiology: (1) covalent bonds, which can be either polar or non-polar, (2) ionic bonds, and (3) hydrogen bonds. There are other types of interactions such as *London* dispersion forces and *van der Waals* forces that could also be discussed when describing the physical and chemical properties of the intermolecular interactions of atoms, but we will not include descriptions of these forces here.

Chemical bonding is determined by the outermost shell of electrons, called the valence electrons (VE), of an atom. The number of VE is important when determining the number and type of chemical bonds an atom will form.

## Covalent Bonds

The strongest chemical bond between two or more atoms is a **covalent bond**. These bonds form when an electron is shared between two atoms, and these are the most common form of chemical bond in living organisms. Covalent bonds form between the atoms of elements that make up the biological molecules in our cells. An example of a simple molecule formed with covalent bonds is water, $H_2O$, with one VE per H atom and 6 VE per O atom. Because of the VE configuration, each H atom is able to accept one additional VE and each O atom is able to accept two additional VE. When sharing electrons, the hydrogen and oxygen atoms that combine to form water molecules become bonded together by covalent bonds (Figure $A.2$). The electron from the hydrogen atom divides its time between the outer electron shell of the hydrogen atom and the outermost electron shell of the oxygen atom. To completely fill the outer shell of an oxygen atom, two electrons from two hydrogen atoms are needed, hence the subscript “2” indicating two atoms of H in a molecule of $H_2O$. This sharing is a lower energy state for all of the atoms involved than if they existed without their outer shells filled.

There are two types of covalent bonds: polar and nonpolar. **Nonpolar covalent** bonds form between two atoms of the same or different elements that share the electrons equally (Figure $A.2$). In a **polar covalent bond**, the electrons shared by the atoms spend more time closer to one nucleus than to the other nucleus. Because of the unequal distribution of electrons between the different nuclei, a slightly positive (δ+) or slightly negative (δ–) charge develops. Water is an example of a molecule formed with **polar covalent bonds** (Figure $A.2$).

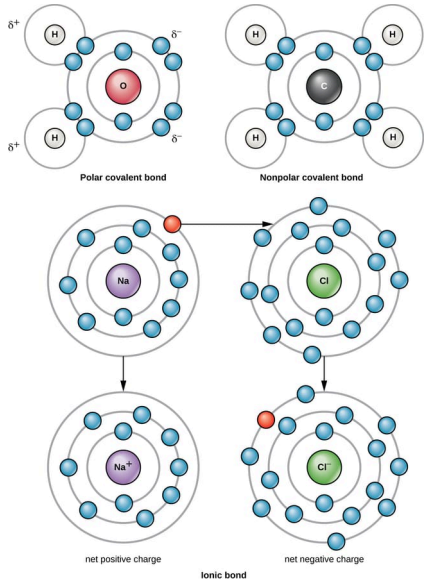



Figure $A.2$: The water molecule (top left) depicts a polar bond with a slightly positive charge on the hydrogen atoms and a slightly negative charge on the oxygen. Methane (top right) is an example of a nonpolar covalent bond. Sodium chloride (bottom) is a substance formed from ionic bonds between sodium and chlorine.

## Ions and Ionic Bonds

When an atom does not contain equal numbers of protons and electrons, it is called an **ion**. Because the number of electrons does not equal the number of protons, each ion has a net charge. Positive ions are formed by losing electrons and are called **cations**. Negative ions are formed by gaining electrons and are called **anions**.

For example, a sodium atom has only has one electron in its outermost shell. It takes less energy for the sodium atom to donate that one electron than it does to accept seven more electrons, which it would need to fill its outer shell. If the sodium atom loses an electron, it now has 11 protons and only 10 electrons, leaving it with an overall charge of +1. It is now called a sodium ion ($Na^+$).

A chlorine atom has seven electrons in its outer shell. Again, it is more energy efficient for the chlorine atom to gain one electron than to lose seven. Therefore, it will more likely gain an electron to form an ion with 17 protons and 18 electrons, giving it a net negative (–1) charge. It is now called a chloride ion ($Cl^-$). This movement of electrons from one atom to another is referred to as electron transfer. Because positive and negative charges attract, these ions stay together and form an **ionic bond**, or a bond between ions. When $Na^+$ and $Cl^-$ ions combine to produce NaCl, an electron from a sodium atom stays with the other seven from the chlorine atom, and the sodium and chloride ions attract each other in a lattice of ions with a net zero charge (Figure $A.2$).

**Polyatomic ions** consist of multiple atoms joined by covalent bonds; but unlike a molecule, a polyatomic ion has a positive or negative charge. It behaves as a cation or anion and can therefore form ionic bonds with other ions to form ionic compounds. The atoms in a polyatomic ion may be from the same element or different elements.

Table $A.1$ lists some cations and anions that commonly occur in microbiology. Note that this table includes monoatomic as well as polyatomic ions.

*Table $A.1$: Some Common Ions in Microbiology*

| Cations | | Anions | |
|---|---|---|---|
| sodium | $Na^+$ | chloride | $Cl^-$ |
| hydrogen | $H^+$ | bicarbonate | $HCO_3^-$ |
| potassium | $K^+$ | carbonate | $CO_3^{2-}$ |
| ammonium | $NH_4^+$ | hydrogen sulfate | $H_2SO_4^{2-}$ |

| Cations | | Anions | |
|---|---|---|---|
| copper (I) | $Cu^{+}$ | hydrogen sulfide | $HS^{-}$ |
| copper (II) | $Cu^{2+}$ | hydroxide | $OH^{-}$ |
| iron (II) | $Fe^{2+}$ | hypochlorite | $ClO^{-}$ |
| iron (III) | $Fe^{3+}$ | nitrite | $NO_2^{-}$ |
| | | nitrate | $NO_3^{-}$ |
| | | peroxide | $O_2^{2-}$ |
| | | phosphate | $PO_4^{3-}$ |
| | | pyrophosphate | $P_2O_7^{4-}$ |
| | | sulfite | $SO_3^{2-}$ |
| | | thiosulfate | $S_2O_3^{2-}$ |

## Molecular Formula, Molecular Mass, and the Mole

For molecules formed by covalent bonds, the molecular formula represents the number and types of elemental atoms that compose the molecule. As an example, consider a molecule of glucose, which has the molecular formula $C_6H_{12}O_6$. This molecular formula indicates that a single molecule of glucose is formed from six carbon atoms, twelve hydrogen atoms, and six oxygen atoms.

The **molecular mass** of a molecule can be calculated using the molecular formula and the atomic mass of each element in the molecule. The number of each type of atom is multiplied by the atomic mass; then the products are added to get the molecular mass. For example the molecular mass of glucose, $C_6H_{12}O_6$ (Figure $A.3$), is calculated as:

$$\begin{aligned} &\text{mass of carbon} && = 12\ \tfrac{\text{amu}}{\text{atom}} \times 6\ \text{atoms} = 72\ \text{amu} \\ &\text{mass of hydrogen} && = 1\ \tfrac{\text{amu}}{\text{atom}} \times 12\ \text{atoms} = 12\ \text{amu} \\ &\text{mass of oxygen} && = 16\ \tfrac{\text{amu}}{\text{atom}} \times 6\ \text{atoms} = 96\ \text{amu} \\ &\text{molecular mass of glucose} && = 72\ \text{amu} + 12\ \text{amu} + 96\ \text{amu} = 180\ \text{amu} \end{aligned} \tag{A.1}$$

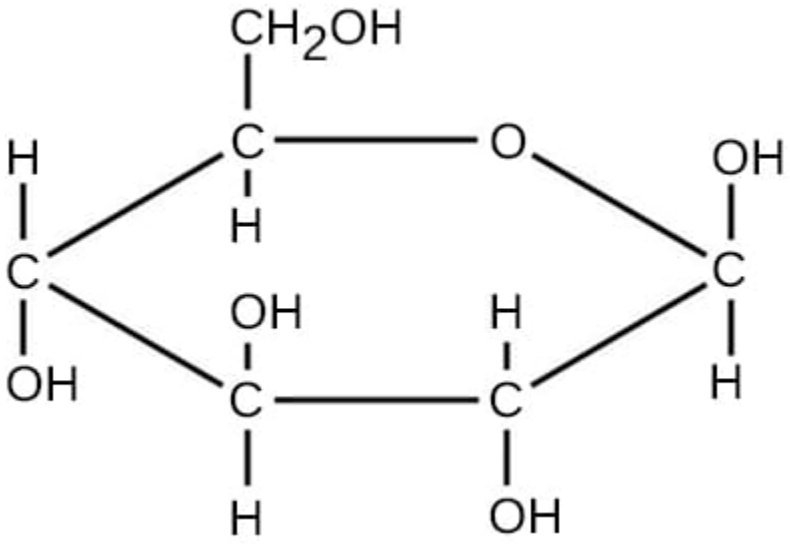



Figure $A.3$: The molecular structure of glucose showing the numbers of carbon, oxygen, and hydrogen atoms. Glucose has a molecular mass of 180 amu.

The number of entities composing a mole has been experimentally determined to be $6.022 \times 10^{23}$, a fundamental constant named

**Avogadro's number** (NA) or the Avogadro constant. This constant is properly reported with an explicit unit of "per mole."

## Energy

Thermodynamics refers to the study of energy and energy transfer involving physical matter.

Matter participating in a particular case of energy transfer is called a system, and everything outside of that matter is called the surroundings. There are two types of systems: open and closed. In an **open system**, energy can be exchanged with its surroundings. A **closed system** cannot exchange energy with its surroundings. Biological organisms are open systems. Energy is exchanged between them and their surroundings as they use energy from the sun to perform photosynthesis or consume energy-storing molecules and release energy to the environment by doing work and releasing heat. Like all things in the physical world, energy is subject to physical laws. In general, energy is defined as the ability to do work, or to create some kind of change. Energy exists in different forms. For example, electrical energy, light energy, and heat energy are all different types of energy. The **first law of thermodynamics,** often referred to as the law of conservation of energy, states that the total amount of energy in the universe is constant and conserved. Energy exists in many different forms. According to the first law of thermodynamics, energy may be transferred from place to place or transformed into different forms, but it cannot be created or destroyed.

The challenge for all living organisms is to obtain energy from their surroundings in forms that they can transfer or transform into usable energy to do work. Microorganisms have evolved to meet this challenge. Chemical energy stored within organic molecules such as sugars and fats is transferred and transformed through a series of cellular chemical reactions into energy within molecules of ATP. Energy in ATP molecules is easily accessible to do work. Examples of the types of work that cells need to do include building complex molecules, transporting materials, powering the motion of cilia or flagella, and contracting muscle fibers to create movement.

A microorganism's primary tasks of obtaining, transforming, and using energy to do work may seem simple. However, the **second law of thermodynamics** explains why these tasks are more difficult than they appear. All energy transfers and transformations are never completely efficient. In every energy transfer, some amount of energy is lost in a form that is unusable. In most cases, this form is **heat energy**. Thermodynamically, heat energy is defined as the energy transferred from one system to another that is not work. For example, some energy is lost as heat energy during cellular metabolic reactions.

The more energy that is lost by a system to its surroundings, the less ordered and more random the system is. Scientists refer to the measure of randomness or disorder within a system as **entropy**. High entropy means high disorder and low energy. Molecules and chemical reactions have varying entropy as well. For example, entropy increases as molecules at a high concentration in one place diffuse and spread out. The second law of thermodynamics says that energy will always be lost as heat in energy transfers or transformations. Microorganisms are highly ordered, requiring constant energy input to be maintained in a state of low entropy.

## Chemical Reactions

**Chemical reactions** occur when two or more atoms bond together to form molecules or when bonded atoms are broken apart. The substances used in a chemical reaction are called the **reactants** (usually found on the left side of a chemical equation), and the substances produced by the reaction are known as the **products** (usually found on the right side of a chemical equation). An arrow is typically drawn between the reactants and products to indicate the direction of the chemical reaction; this direction is not always a "one-way street."

An example of a simple chemical reaction is the breaking down of hydrogen peroxide molecules, each of which consists of two hydrogen atoms bonded to two oxygen atoms ($H_2O_2$). The reactant hydrogen peroxide is broken down into water, containing one oxygen atom bound to two hydrogen atoms ($H_2O$), and oxygen, which consists of two bonded oxygen atoms ($O_2$). In the equation below, the reaction includes two hydrogen peroxide molecules and two water molecules. This is an example of a balanced chemical equation, wherein the number of atoms of each element is the same on each side of the equation. According to the law of conservation of matter, the number of atoms before and after a chemical reaction should be equal, such that no atoms are, under normal circumstances, created or destroyed.

$$2\,\mathrm{H_2O_2}\,(\mathrm{hydrogen\ \ peroxide}) \longrightarrow 2\,\mathrm{H_2O}\,(\mathrm{water}) + \mathrm{O_2}\,(\mathrm{oxygen}) \tag{A.2}$$

Some chemical reactions, such as the one shown above, can proceed in one direction until the reactants are all used up. Equations that describe these reactions contain a unidirectional arrow and are irreversible. **Reversible reactions** are those that can go in either direction. In reversible reactions, reactants are turned into products, but when the concentration of product rises

above a certain threshold (characteristic of the particular reaction), some of these products will be converted back into reactants; at this point, the designations of products and reactants are reversed. The changes in concentration continue until a certain relative balance in concentration between reactants and products occurs—a state called **chemical equilibrium**. At this point, both the forward and reverse reactions continue to occur, but they do so at the same rate, so the concentrations of reactants and products do not change. These situations of reversible reactions are often denoted by a chemical equation with a double-headed arrow pointing towards both the reactants and products. For example, when carbon dioxide dissolves in water, it can do so as a gas dissolved in water *or* by reacting with water to produce carbonic acid. In the cells of some microorganisms, the rate of carbonic acid production is accelerated by the enzyme carbonic anhydrase, as indicated in the following equation:

$$\mathrm{CO_2 + H_2O \overset{\overset{carbonic}{anhydrase}}{\rightleftharpoons} H_2CO_3 \rightleftharpoons H^+ + HCO_3^-} \tag{A.3}$$

## Properties of Water and Solutions

The hydrogen and oxygen atoms within water molecules form polar covalent bonds. There is no overall charge to a water molecule, but there is one $\partial^+$ on each hydrogen atom and two $\partial^-$ on the oxygen atom. Each water molecule attracts other water molecules because of the positive and negative charges in the different parts of the molecule (Figure $A.4$). Water also attracts other polar molecules (such as sugars), forming hydrogen bonds. When a substance readily forms hydrogen bonds with water, it can dissolve in water and is referred to as **hydrophilic** ("water-loving"). Hydrogen bonds are not readily formed with nonpolar substances like oils and fats. These nonpolar compounds are **hydrophobic** ("water-fearing") and will orient away from and avoid water.

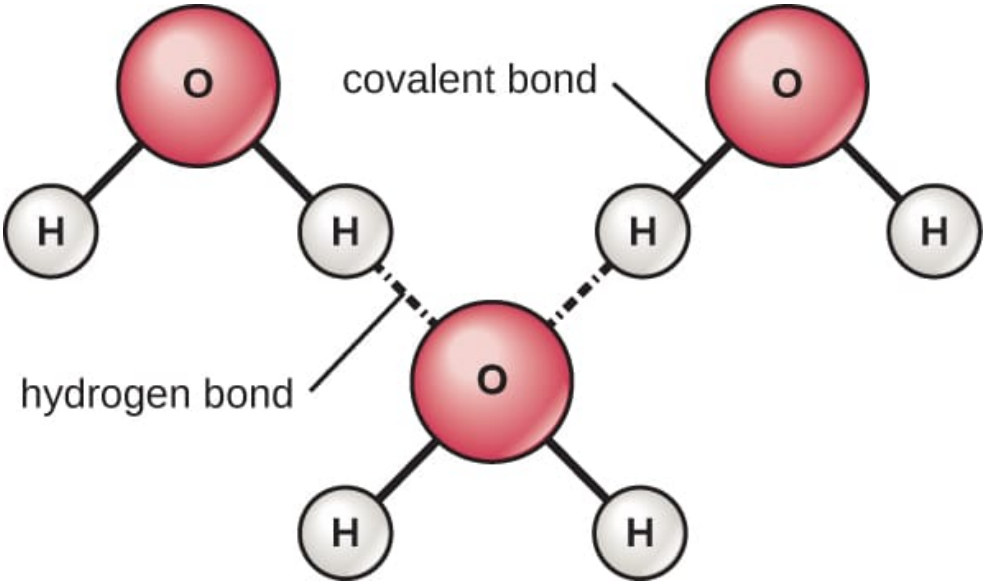



Figure $A.4$: Hydrogen bonds form between slightly positive (∂+) and slightly negative (∂–) charges of polar covalent molecules such as water.

The hydrogen bonds in water allow it to absorb and release heat energy more slowly than many other substances. This means that water moderates temperature changes within organisms and in their environments. As energy input continues, the balance between hydrogen-bond formation and breaking swings toward fewer hydrogen bonds: more bonds are broken than are formed. This process results in the release of individual water molecules at the surface of the liquid (such as a body of water, the leaves of a plant, or the skin of an organism) in a process called **evaporation**.

Conversely, as molecular motion decreases and temperatures drop, less energy is present to break the hydrogen bonds between water molecules. These bonds remain intact and begin to form a rigid, lattice-like structure (e.g., ice). When frozen, ice is less dense (the molecules are farther apart) than liquid water. This means that ice floats on the surface of a body of water. In lakes, ponds, and oceans, ice will form on the surface of the water, creating an insulating barrier to protect the animal and plant life beneath from freezing in the water. If this did not happen, plants and animals living in water would freeze in a block of ice and could not move freely, making life in cold temperatures difficult or impossible.

Because water is polar, with slight positive and negative charges, ionic compounds and polar molecules can readily dissolve in it. Water is, therefore, what is referred to as a solvent—a substance capable of dissolving another substance. The charged particles will form hydrogen bonds with a surrounding layer of water molecules. This is referred to as a **sphere of hydration** and serves to

keep the ions separated or dispersed in the water (Figure $A.5$). These spheres of hydration are also referred to as hydration shells. The polarity of the water molecule makes it an effective solvent and is important in its many roles in living systems.

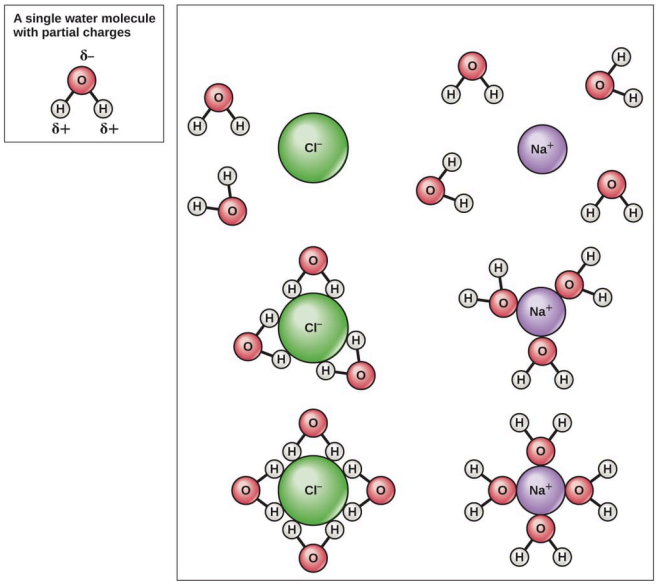



Figure $A.5$: When table salt (NaCl) is mixed in water, spheres of hydration form around the ions.

The ability of insects to float on and skate across pond water results from the property of **cohesion**. In cohesion, water molecules are attracted to each other (because of hydrogen bonding), keeping the molecules together at the liquid-air (gas) interface. Cohesion gives rise to surface tension, the capacity of a substance to withstand rupture when placed under tension or stress.

These cohesive forces are also related to water's property of **adhesion**, or the attraction between water molecules and other molecules. This is observed when water "climbs" up a straw placed in a glass of water. You will notice that the water appears to be higher on the sides of the straw than in the middle. This is because the water molecules are attracted to the straw and therefore adhere to it.

Cohesion and adhesion are also factors in bacterial colonies and biofilm formation. Cohesion keeps the colony intact (helps it "stick" to a surface), while adhesion keeps the cells adhered to each other. Cohesive and adhesive forces are important for sustaining life. For example, because of these forces, water in natural surroundings provides the conditions necessary to allow bacterial and archaeal cells to adhere and accumulate on surfaces.

## Acids and Bases

The **pH** of a solution is a measure of hydrogen ion ($H^+$) and hydroxide ion ($OH^-$) concentrations and is described as **acidity** or **alkalinity,** respectively. Acidity and alkalinity (also referred to as basicity) can be measured and calculated. pH can be simply represented by the mathematic equation, $\mathrm{pH} = -\log_{10}[\mathrm{H}^+]$. On the left side of the equation, the "p" means "the negative logarithm of " and the H represents the [$H^+$]. On the right side of the equation, [$H^+$] is the concentration of $H^+$ in moles/L . What is not represented in this simple equation is the contribution of the $OH^-$, which also participates in acidity or alkalinity. Calculation of pH results in a number range of 0 to 14 called the pH scale (Figure $A.6$). A pH value between 0 and 6.9 indicates an acid. It is also referred to as a low pH, due to a high [$H^+$] and low [$OH^-$] concentration. A pH value between 7.1 and 14 indicates an alkali or base. It is also referred to as a high pH, due to a low [$H^+$] and high [$OH^-$] concentration. A pH of 7 is described as a neutral pH and occurs when [$H^+$] equals [$OH^-$].

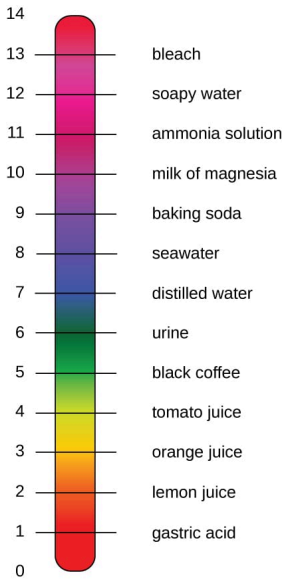



Figure $A.6$: The pH scale measures the concentration of hydrogen ions [$H^+$] and [$OH^-$] in a substance. (credit: modification of work by Edward Stevens)

A change of one unit on the pH scale represents a change in the [$H^+$] by a factor of 10, a change in two units represents a change in the [$H^+$] by a factor of 100. Thus, small changes in pH represent large changes in [$H^+$].

## Footnotes

1. 1 Schrijver, Karel, and Iris Schrijver. *Living with the Stars: How the Human Body Is Connected to the Life Cycles of the Earth, the Planets, and the Stars*. Oxford University Press, USA, 2015.
2. 2 National Oceanic and Atmospheric Administration, “Stable and Radiocarbon Isotopes of Carbon Dioxide.” Web page. Accessed Feb 19, 2016 [http://www.esrl.noaa.gov/gmd/outreac...hemistry.html]
3. 3 ibid.
4. 4 ibid.

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# B: Mathematical Basics

## Squares and Other Powers

An exponent, or a power, is mathematical shorthand for repeated multiplications. For example, the exponent "2" means to multiply the base for that exponent by itself (in the example here, the base is "5"):

$$5^2 = 5 \times 5 = 25 \tag{B.1}$$

The exponent is "2" and the base is the number "5." This expression (multiplying a number by itself) is also called a square. Any number raised to the power of 2 is being squared. Any number raised to the power of 3 is being cubed:

$$5^3 = 5 \times 5 \times 5 = 125 \tag{B.2}$$

A number raised to the fourth power is equal to that number multiplied by itself four times, and so on for higher powers. In general:

$$n^x = n \times n^{x-1} \tag{B.3}$$

## Calculating Percents

A percent is a way of expressing a fractional amount of something using a whole divided into 100 parts. A percent is a ratio whose denominator is 100. We use the percent symbol, %, to show percent. Thus, 25% means a ratio of $\frac{25}{100}$, 3% means a ratio of $\frac{3}{100}$, and 100% percent means $\frac{100}{100}$, or a whole.

### Converting Percents

A percent can be converted to a fraction by writing the value of the percent as a fraction with a denominator of 100 and simplifying the fraction if possible.

$$25\% = \frac{25}{100} = \frac{1}{4} \tag{B.4}$$

A percent can be converted to a decimal by writing the value of the percent as a fraction with a denominator of 100 and dividing the numerator by the denominator.

$$10\% = \frac{10}{100} = 0.10 \tag{B.5}$$

To convert a decimal to a percent, write the decimal as a fraction. If the denominator of the fraction is not 100, convert it to a fraction with a denominator of 100, and then write the fraction as a percent.

$$0.833 = \frac{833}{1000} = \frac{83.3}{100} = 83.3\% \tag{B.6}$$

To convert a fraction to a percent, first convert the fraction to a decimal, and then convert the decimal to a percent.

$$\frac{3}{4} = 0.75 = \frac{75}{100} = 75\% \tag{B.7}$$

Suppose a researcher finds that 15 out of 23 students in a class are carriers of *Neisseria meningitides*. What percentage of students are carriers? To find this value, first express the numbers as a fraction.

$$\frac{\text{carriers}}{\text{total students}} = \frac{15}{23} \tag{B.8}$$

Then divide the numerator by the denominator.

$$\frac{15}{23} = 15 \div 23 \approx 0.65 \tag{B.9}$$

Finally, to convert a decimal to a percent, multiply by 100.

$$0.65 \times 100 = 65\% \tag{B.10}$$

The percent of students who are carriers is 65%.

You might also get data on occurrence and non-occurrence; for example, in a sample of students, 9 tested positive for *Toxoplasma* antibodies, while 28 tested negative. What is the percentage of seropositive students? The first step is to determine the "whole," of which the positive students are a part. To do this, sum the positive and negative tests.

$$\text{positive} + \text{negative} = 9 + 28 = 37 \tag{B.11}$$

The whole sample consisted of 37 students. The fraction of positives is:

$$\frac{\text{positive}}{\text{total students}} = \frac{9}{37} \tag{B.12}$$

To find the percent of students who are carriers, divide the numerator by the denominator and multiply by 100.

$$\begin{gathered}\frac{9}{37} = 9 \div 37 \approx 0.24 \\ 0.24 \times 100 = 24\%\end{gathered} \tag{B.13}$$

The percent of positive students is about 24%.

Another way to think about calculating a percent is to set up equivalent fractions, one of which is a fraction with 100 as the denominator, and cross-multiply. The previous example would be expressed as:

$$\frac{9}{37} = \frac{x}{100} \tag{B.14}$$

Now, cross multiply and solve for the unknown:

$$\begin{aligned} 9 \times 100 &= 37x \\ \frac{9 \times 100}{37} &= x && \text{Divide both sides by } 37 \\ \frac{900}{37} &= x && \text{Multiply} \\ 24 &\approx x && \text{Divide} \end{aligned}$$

The answer, rounded, is the same.

## Multiplying and Dividing by Tens

In many fields, especially in the sciences, it is common to multiply decimals by powers of 10. Let's see what happens when we multiply 1.9436 by some powers of 10.

$$\begin{aligned} 1.9436(10) &= 19.436 \\ 1.9436(100) &= 194.36 \\ 1.9436(1000) &= 1943.6 \end{aligned}$$

The number of places that the decimal point moves is the same as the number of zeros in the power of ten. Table $B.1$ summarizes the results.

*Table* $B.1$

| Multiply by | Zeros | Decimal point moves . . . |
|---|---|---|
| 10 | 1 | 1 place to the right |
| 100 | 2 | 2 places to the right |
| 1,000 | 3 | 3 places to the right |
| 10,000 | 4 | 4 places to the right |

We can use this pattern as a shortcut to multiply by powers of ten instead of multiplying using the vertical format. We can count the zeros in the power of 10 and then move the decimal point that same number of places to the right.

So, for example, to multiply 45.86 by 100, move the decimal point 2 places to the right.

$$45.86 \times 100 = 4586.$$



Sometimes when we need to move the decimal point, there are not enough decimal places. In that case, we use zeros as placeholders. For example, let's multiply 2.4 by 100. We need to move the decimal point 2 places to the right. Since there is only one digit to the right of the decimal point, we must write a 0 in the hundredths place.

$$2.4 \times 100 = 240.$$



When dividing by powers of 10, simply take the opposite approach and move the decimal to the left by the number of zeros in the power of ten.

Let's see what happens when we divide 1.9436 by some powers of 10.

$$1.9436 \div 10 = 0.19436$$
$$1.9436 \div 100 = 0.019436$$
$$1.9436 \div 1000 = 0.0019436$$

If there are insufficient digits to move the decimal, add zeroes to create places.

## Scientific Notation

Scientific notation is used to express very large and very small numbers as a product of two numbers. The first number of the product, the digit term, is usually a number not less than 1 and not greater than 10. The second number of the product, the exponential term, is written as 10 with an exponent. Some examples of scientific notation are given in Table $B.2$.

*Table* $B.2$

| Standard Notation | Scientific Notation |
|---|---|
| 1000 | $1 \times 10^3$ |
| 100 | $1 \times 10^2$ |
| 10 | $1 \times 10^1$ |
| 1 | $1 \times 10^0$ |

| Standard Notation | Scientific Notation |
|---|---|
| 0.1 | $1 \times 10^{-1}$ |
| 0.01 | $1 \times 10^{-2}$ |

Scientific notation is particularly useful notation for very large and very small numbers, such as 1,230,000,000 = $1.23 \times 10^{9}$, and 0.000000000036 = $3.6 \times 10^{-10}$.

## Expressing Numbers in Scientific Notation

Converting any number to scientific notation is straightforward. Count the number of places needed to move the decimal next to the left-most non-zero digit: that is, to make the number between 1 and 10. Then multiply that number by 10 raised to the number of places you moved the decimal. The exponent is positive if you moved the decimal to the left and negative if you moved the decimal to the right. So

$$2386 = 2.386 \times 1000 = 2.386 \times 10^{3} \tag{B.15}$$

and

$$0.123 = 1.23 \times 0.1 = 1.23 \times 10^{-1} \tag{B.16}$$

The power (exponent) of 10 is equal to the number of places the decimal is shifted.

## Logarithms

The common logarithm (log) of a number is the power to which 10 must be raised to equal that number. For example, the common logarithm of 100 is 2, because 10 must be raised to the second power to equal 100. Additional examples are in Table $B.3$.

*Table $B.3$*

| Number | Exponential Form | Common Logarithm |
|---|---|---|
| 1000 | $10^{3}$ | 3 |
| 10 | $10^{1}$ | 1 |
| 1 | $10^{0}$ | 0 |
| 0.1 | $10^{-1}$ | –1 |
| 0.001 | $10^{-3}$ | –3 |

To find the common logarithm of most numbers, you will need to use the LOG button on a calculator.

## Rounding and Significant Digits

In reporting numerical data obtained via measurements, we use only as many significant figures as the accuracy of the measurement warrants. For example, suppose a microbiologist using an automated cell counter determines that there are 525,341 bacterial cells in a one-liter sample of river water. However, she records the concentration as 525,000 cells per liter and uses this rounded number to estimate the number of cells that would likely be found in 10 liters of river water. In this instance, the last three digits of the measured quantity are not considered *significant*. They are rounded to account for variations in the number of cells that would likely occur if more samples were measured.

The importance of significant figures lies in their application to fundamental computation. In addition and subtraction, the sum or difference should contain as many digits to the right of the decimal as that in the *least* certain (indicated by underscoring in the following example) of the numbers used in the computation.

Suppose a microbiologist wishes to calculate the total mass of two samples of agar.

$$\begin{array}{r} 4.38\underline{3}\ \text{g} \\ 3.002\underline{1}\ \text{g} \\ \hline 7.38\underline{5}\ \text{g} \end{array} \tag{B.17}$$

The least certain of the two masses has three decimal places, so the sum must have three decimal places.

In multiplication and division, the product or quotient should contain no more digits than than in the factor containing the *least* number of significant figures. Suppose the microbiologist would like to calculate how much of a reagent would be present in 6.6 mL if the concentration is 0.638 g/mL.

$$0.63\underline{8}\ \frac{\text{g}}{\text{mL}} \times 6.\underline{6}\ \text{mL} = 4.1\ \text{g} \tag{B.18}$$

Again, the answer has only one decimal place because this is the accuracy of the least accurate number in the calculation.

When rounding numbers, increase the retained digit by 1 if it is followed by a number larger than 5 (“round up”). Do not change the retained digit if the digits that follow are less than 5 (“round down”). If the retained digit is followed by 5, round up if the retained digit is odd, or round down if it is even (after rounding, the retained digit will thus always be even).

## Generation Time

It is possible to write an equation to calculate the cell numbers at any time if the number of starting cells and doubling time are known, as long as the cells are dividing at a constant rate. We define $N_0$ as the starting number of bacteria, the number at time $t = 0$. $N_i$ is the number of bacteria at time $t = i$, an arbitrary time in the future. Finally we will set $j$ equal to the number of generations, or the number of times the cell population doubles during the time interval. Then we have,

$$N_i = N_0 \times 2^j \tag{B.19}$$

This equation is an expression of growth by binary fission.

In our example, $N_0 = 4$, the number of generations, $j$, is equal to 3 after 90 minutes because the generation time is 30 minutes. The number of cells can be estimated from the following equation:

$$\begin{aligned} N_i &= N_0 \times 2^j \\ N_{90} &= 4 \times 2^3 \\ N_{90} &= 4 \times 8 = 32 \end{aligned}$$

The number of cells after 90 minutes is 32.

## Most Probable Number

The table in Figure $B.1$ contains values used to calculate the most probable number example given in How Microbes Grow.

| Most Probable Number Table | | | | | |
|---|---|---|---|---|---|
| Number of tubes giving a positive reaction for a 5-tube set | | | MPN (per 100 ml) | 95% Confidence Limits | |
| *10 ml* | *1 ml* | *0.1 ml* | | *Low* | *High* |
| 0 | 0 | 0 | <2 | <1 | 7 |
| 0 | 1 | 0 | 2 | <1 | 7 |
| 0 | 2 | 0 | 4 | <1 | 11 |
| 1 | 0 | 0 | 2 | <1 | 7 |
| 1 | 0 | 1 | 4 | <1 | 11 |
| 1 | 1 | 0 | 4 | <1 | 11 |
| 1 | 1 | 1 | 6 | <1 | 15 |
| 2 | 0 | 0 | 5 | <1 | 13 |
| 2 | 0 | 1 | 7 | 1 | 17 |
| 2 | 1 | 0 | 7 | 1 | 17 |
| 2 | 1 | 1 | 9 | 2 | 21 |
| 2 | 2 | 0 | 9 | 2 | 21 |
| 2 | 3 | 0 | 12 | 3 | 28 |
| 3 | 0 | 0 | 8 | 1 | 19 |
| 3 | 0 | 1 | 11 | 2 | 25 |
| 3 | 1 | 0 | 11 | 2 | 25 |
| 3 | 1 | 1 | 14 | 4 | 34 |
| 3 | 2 | 0 | 14 | 4 | 34 |
| 3 | 2 | 1 | 17 | 5 | 46 |
| 3 | 3 | 0 | 17 | 5 | 46 |
| 4 | 0 | 0 | 13 | 3 | 31 |
| 4 | 0 | 1 | 17 | 5 | 46 |
| 4 | 1 | 0 | 17 | 5 | 46 |
| 4 | 1 | 1 | 21 | 7 | 63 |
| 4 | 1 | 2 | 26 | 9 | 78 |
| 4 | 2 | 0 | 22 | 7 | 67 |
| 4 | 2 | 1 | 26 | 9 | 78 |
| 4 | 3 | 0 | 27 | 9 | 80 |
| 4 | 3 | 1 | 33 | 11 | 93 |
| 4 | 4 | 0 | 34 | 12 | 93 |
| 5 | 0 | 0 | 23 | 7 | 70 |
| 5 | 0 | 1 | 31 | 11 | 89 |
| 5 | 0 | 2 | 43 | 15 | 110 |
| 5 | 1 | 0 | 33 | 11 | 93 |
| 5 | 1 | 1 | 46 | 16 | 120 |
| 5 | 1 | 2 | 63 | 21 | 150 |
| 5 | 2 | 0 | 49 | 17 | 130 |
| 5 | 2 | 1 | 70 | 23 | 170 |
| 5 | 2 | 2 | 94 | 28 | 220 |
| 5 | 3 | 0 | 79 | 25 | 190 |
| 5 | 3 | 1 | 110 | 31 | 250 |
| 5 | 3 | 2 | 140 | 37 | 340 |
| 5 | 3 | 3 | 180 | 44 | 500 |

Figure $B.1$

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# GLOSSARY

## S

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