**Chapter 21**

**Skin and Eye Infections**

*Figure 21.1* The skin is an important barrier to pathogens, but it can also develop infections. These raised lesions (left) are typical of folliculitis, a condition that results from the inflammation of hair follicles. Acne lesions (right) also result from inflammation of hair follicles. In this case, the inflammation results when hair follicles become clogged with complex lipids, fatty acids, and dead skin cells, producing a favorable environment for bacteria.

**Chapter Outline**

- 21.1 Anatomy and Normal Microbiota of the Skin and Eyes
- 21.2 Bacterial Infections of the Skin and Eyes
- 21.3 Viral Infections of the Skin and Eyes
- 21.4 Mycoses of the Skin
- 21.5 Protozoan and Helminthic Infections of the Skin and Eyes

**Introduction**

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.
21.1 Anatomy and Normal Microbiota of the Skin and Eyes

Learning Objectives

• Describe the major anatomical features of the skin and eyes
• Compare and contrast the microbiomes of various body sites, such as the hands, back, feet, and eyes
• Explain how microorganisms overcome defenses of skin and eyes in order to cause infection
• Describe general signs and symptoms of disease associated with infections of the skin and eyes

Human skin is an important part of the innate immune system. In addition to serving a wide range of other functions, the skin serves as an important barrier to microbial invasion. Not only is it a physical barrier to penetration of deeper tissues by potential pathogens, but it also provides an inhospitable environment for the growth of many pathogens. In this section, we will provide a brief overview of the anatomy and normal microbiota of the skin and eyes, along with general symptoms associated with skin and eye infections.

Layers of the Skin

Human skin is made up of several layers and sublayers. The two main layers are the **epidermis** and the **dermis**. These layers cover a third layer of tissue called the **hypodermis**, which consists of fibrous and adipose connective tissue (Figure 21.2).

The epidermis is the outermost layer of the skin, and it is relatively thin. The exterior surface of the epidermis, called the **stratum corneum**, primarily consists of dead skin cells. This layer of dead cells limits direct contact between the outside world and live cells. The stratum corneum is rich in **keratin**, a tough, fibrous protein that is also found in hair and nails. Keratin helps make the outer surface of the skin relatively tough and waterproof. It also helps to keep the surface of the skin dry, which reduces microbial growth. However, some microbes are still able to live on the surface of the skin, and some of these can be shed with dead skin cells in the process of **desquamation**, which is the shedding and peeling of skin that occurs as a normal process but that may be accelerated when infection is present.

Beneath the epidermis lies a thicker skin layer called the dermis. The dermis contains connective tissue and embedded structures such as blood vessels, nerves, and muscles. Structures called **hair follicles** (from which hair grows) are located within the dermis, even though much of their structure consists of epidermal tissue. The dermis also contains the two major types of glands found in human skin: **sweat glands** (tubular glands that produce sweat) and **sebaceous glands** (which are associated with hair follicles and produce **sebum**, a lipid-rich substance containing proteins and minerals).

Clinical Focus

Part 1

Sam, a college freshman with a bad habit of oversleeping, nicked himself shaving in a rush to get to class on time. At the time, he didn't think twice about it. But two days later, he noticed the cut was surrounded by a reddish area of skin that was warm to the touch. When the wound started oozing pus, he decided he had better stop by the university's clinic. The doctor took a sample from the lesion and then cleaned the area.

• What type of microbe could be responsible for Sam's infection?

*Jump to the next Clinical Focus box.*
Perspiration (sweat) provides some moisture to the epidermis, which can increase the potential for microbial growth. For this reason, more microbes are found on the regions of the skin that produce the most sweat, such as the skin of the underarms and groin. However, in addition to water, sweat also contains substances that inhibit microbial growth, such as salts, lysozyme, and antimicrobial peptides. Sebum also serves to protect the skin and reduce water loss. Although some of the lipids and fatty acids in sebum inhibit microbial growth, sebum contains compounds that provide nutrition for certain microbes.

Figure 21.2  (a) A micrograph of a section through human skin shows the epidermis and dermis. (b) The major layers of human skin are the epidermis, dermis, and hypodermis. (credit b: modification of work by National Cancer Institute)

Check Your Understanding

- How does desquamation help with preventing infections?

Normal Microbiota of the Skin

The skin is home to a wide variety of normal microbiota, consisting of commensal organisms that derive nutrition from skin cells and secretions such as sweat and sebum. The normal microbiota of skin tends to inhibit transient-microbe colonization by producing antimicrobial substances and outcompeting other microbes that land on the surface of the skin. This helps to protect the skin from pathogenic infection.

The skin’s properties differ from one region of the body to another, as does the composition of the skin’s microbiota. The availability of nutrients and moisture partly dictates which microorganisms will thrive in a particular region of the skin. Relatively moist skin, such as that of the nares (nostrils) and underarms, has a much different microbiota than the dryer skin on the arms, legs, hands, and top of the feet. Some areas of the skin have higher densities of sebaceous glands. These sebum-rich areas, which include the back, the folds at the side of the nose, and the back of the neck, harbor distinct microbial communities that are less diverse than those found on other parts of the body.
Different types of bacteria dominate the dry, moist, and sebum-rich regions of the skin. The most abundant microbes typically found in the dry and sebaceous regions are Betaproteobacteria and Propionibacteria, respectively. In the moist regions, *Corynebacterium* and *Staphylococcus* are most commonly found (Figure 21.3). Viruses and fungi are also found on the skin, with *Malassezia* being the most common type of fungus found as part of the normal microbiota. The role and populations of viruses in the microbiota, known as viromes, are still not well understood, and there are limitations to the techniques used to identify them. However, Circoviridae, Papillomaviridae, and Polyomaviridae appear to be the most common residents in the healthy skin virome.  

![Figure 21.3](credit: modification of work by National Human Genome Research Institute)

**Check Your Understanding**

- What are the four most common bacteria that are part of the normal skin microbiota?

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Infections of the Skin

While the microbiota of the skin can play a protective role, it can also cause harm in certain cases. Often, an opportunistic pathogen residing in the skin microbiota of one individual may be transmitted to another individual more susceptible to an infection. For example, methicillin-resistant *Staphylococcus aureus* (MRSA) can often take up residence in the nares of health care workers and hospital patients; though harmless on intact, healthy skin, MRSA can cause infections if introduced into other parts of the body, as might occur during surgery or via a post-surgical incision or wound. This is one reason why clean surgical sites are so important.

Injury or damage to the skin can allow microbes to enter deeper tissues, where nutrients are more abundant and the environment is more conducive to bacterial growth. Wound infections are common after a puncture or laceration that damages the physical barrier of the skin. Microbes may infect structures in the dermis, such as hair follicles and glands, causing a localized infection, or they may reach the bloodstream, which can lead to a systemic infection.

In some cases, infectious microbes can cause a variety of rashes or lesions that differ in their physical characteristics. These rashes can be the result of inflammation reactions or direct responses to toxins produced by the microbes. Table 21.1 lists some of the medical terminology used to describe skin lesions and rashes based on their characteristics; Figure 21.4 and Figure 21.5 illustrate some of the various types of skin lesions. It is important to note that many different diseases can lead to skin conditions of very similar appearance; thus the terms used in the table are generally not exclusive to a particular type of infection or disease.

### Some Medical Terms Associated with Skin Lesions and Rashes

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>abscess</td>
<td>localized collection of pus</td>
</tr>
<tr>
<td>bulla (pl., bullae)</td>
<td>fluid-filled blister no more than 5 mm in diameter</td>
</tr>
<tr>
<td>carbuncle</td>
<td>deep, pus-filled abscess generally formed from multiple furuncles</td>
</tr>
<tr>
<td>crust</td>
<td>dried fluids from a lesion on the surface of the skin</td>
</tr>
<tr>
<td>cyst</td>
<td>encapsulated sac filled with fluid, semi-solid matter, or gas, typically located just below the upper layers of skin</td>
</tr>
<tr>
<td>folliculitis</td>
<td>a localized rash due to inflammation of hair follicles</td>
</tr>
<tr>
<td>furuncle (boil)</td>
<td>pus-filled abscess due to infection of a hair follicle</td>
</tr>
<tr>
<td>macules</td>
<td>smooth spots of discoloration on the skin</td>
</tr>
<tr>
<td>papules</td>
<td>small raised bumps on the skin</td>
</tr>
<tr>
<td>pseudocyst</td>
<td>lesion that resembles a cyst but with a less defined boundary</td>
</tr>
<tr>
<td>purulent</td>
<td>pus-producing; suppurative</td>
</tr>
<tr>
<td>pustules</td>
<td>fluid- or pus-filled bumps on the skin</td>
</tr>
<tr>
<td>pyoderma</td>
<td>any suppurative (pus-producing) infection of the skin</td>
</tr>
<tr>
<td>suppurative</td>
<td>producing pus; purulent</td>
</tr>
<tr>
<td>ulcer</td>
<td>break in the skin; open sore</td>
</tr>
<tr>
<td>vesicle</td>
<td>small, fluid-filled lesion</td>
</tr>
<tr>
<td>wheal</td>
<td>swollen, inflamed skin that itches or burns, such as from an insect bite</td>
</tr>
</tbody>
</table>

*Table 21.1*
Figure 21.4  (a) Acne is a bacterial infection of the skin that manifests as a rash of inflamed hair follicles (folliculitis). The large whitehead near the center of the cheek is an infected hair follicle that has become purulent (or suppurative), leading to the formation of a furuncle. (b) An abscess is a pus-filled lesion. (credit b: modification of work by Bruce Blaus)

Figure 21.5  Numerous causes can lead to skin lesions of various types, some of which are very similar in appearance. (credit: modification of work by Bruce Blaus)

Check Your Understanding

- How can asymptomatic health care workers transmit bacteria such as MRSA to patients?

Anatomy and Microbiota of the Eye

Although the eye and skin have distinct anatomy, they are both in direct contact with the external environment. An important component of the eye is the nasolacrimal drainage system, which serves as a conduit for the fluid of the eye, called tears. Tears flow from the external eye to the nasal cavity by the lacrimal apparatus, which is composed of
the structures involved in tear production (Figure 21.6). The **lacrimal gland**, above the eye, secretes tears to keep the eye moist. There are two small openings, one on the inside edge of the upper eyelid and one on the inside edge of the lower eyelid, near the nose. Each of these openings is called a **lacrimal punctum**. Together, these lacrimal puncta collect tears from the eye that are then conveyed through **lacrimal ducts** to a reservoir for tears called the **lacrimal sac**, also known as the dacrocyst or tear sac.

From the sac, tear fluid flows via a **nasolacrimal duct** to the inner nose. Each nasolacrimal duct is located underneath the skin and passes through the bones of the face into the nose. Chemicals in tears, such as defensins, lactoferrin, and lysozyme, help to prevent colonization by pathogens. In addition, mucins facilitate removal of microbes from the surface of the eye.

![Diagram of the lacrimal apparatus](credit: modification of work by "Evidence Based Medical Educator Inc."/YouTube)

The surfaces of the eyeball and inner eyelid are mucous membranes called **conjunctiva**. The normal conjunctival microbiota has not been well characterized, but does exist. One small study (part of the Ocular Microbiome project) found twelve genera that were consistently present in the conjunctiva. These microbes are thought to help defend the membranes against pathogens. However, it is still unclear which microbes may be transient and which may form a stable microbiota.

Use of contact lenses can cause changes in the normal microbiota of the conjunctiva by introducing another surface into the natural anatomy of the eye. Research is currently underway to better understand how contact lenses may impact the normal microbiota and contribute to eye disease.

The watery material inside of the eyeball is called the vitreous humor. Unlike the conjunctiva, it is protected from contact with the environment and is almost always sterile, with no normal microbiota (Figure 21.7).

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Infections of the Eye

The conjunctiva is a frequent site of infection of the eye; like other mucous membranes, it is also a common portal of entry for pathogens. Inflammation of the conjunctiva is called **conjunctivitis**, although it is commonly known as pinkeye because of the pink appearance in the eye. Infections of deeper structures, beneath the cornea, are less common (Figure 21.8). Conjunctivitis occurs in multiple forms. It may be acute or chronic. Acute purulent conjunctivitis is associated with pus formation, while acute hemorrhagic conjunctivitis is associated with bleeding in the conjunctiva. The term **blepharitis** refers to an inflammation of the eyelids, while **keratitis** refers to an inflammation of the cornea (Figure 21.8); **keratoconjunctivitis** is an inflammation of both the cornea and the conjunctiva, and **dacryocystitis** is an inflammation of the lacrimal sac that can often occur when a nasolacrimal duct is blocked.

Infections leading to conjunctivitis, blepharitis, keratoconjunctivitis, or dacryocystitis may be caused by bacteria or viruses, but allergens, pollutants, or chemicals can also irritate the eye and cause inflammation of various structures. Viral infection is a more likely cause of conjunctivitis in cases with symptoms such as fever and watery discharge that occurs with upper respiratory infection and itchy eyes. **Table 21.2** summarizes some common forms of conjunctivitis and blepharitis.
**Types of Conjunctivities and Blepharitis**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
<th>Causative Agent(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute purulent conjunctivitis</td>
<td>Conjunctivitis with purulent discharge</td>
<td>Bacterial (<em>Haemophilus</em>, <em>Staphylococcus</em>)</td>
</tr>
<tr>
<td>Acute hemorrhagic conjunctivitis</td>
<td>Involves subconjunctival hemorrhages</td>
<td>Viral (Picornaviridae)</td>
</tr>
<tr>
<td>Acute ulcerative blepharitis</td>
<td>Infection involving eyelids; pustules and ulcers may develop</td>
<td>Bacterial (<em>Staphylococcal</em>) or viral (herpes simplex, varicella-zoster, etc.)</td>
</tr>
<tr>
<td>Follicular conjunctivitis</td>
<td>Inflammation of the conjunctiva with nodules (dome-shaped structures that are red at the base and pale on top)</td>
<td>Viral (adenovirus and others); environmental irritants</td>
</tr>
<tr>
<td>Dacryocystitis</td>
<td>Inflammation of the lacrimal sac often associated with a plugged nasolacrimal duct</td>
<td>Bacterial (<em>Haemophilus</em>, <em>Staphylococcus</em>, <em>Streptococcus</em>)</td>
</tr>
<tr>
<td>Keratitis</td>
<td>Inflammation of cornea</td>
<td>Bacterial, viral, or protozoal; environmental irritants</td>
</tr>
<tr>
<td>Keratoconjunctivitis</td>
<td>Inflammation of cornea and conjunctiva</td>
<td>Bacterial, viral (adenoviruses), or other causes (including dryness of the eye)</td>
</tr>
<tr>
<td>Nonulcerative blepharitis</td>
<td>Inflammation, irritation, redness of the eyelids without ulceration</td>
<td>Environmental irritants; allergens</td>
</tr>
<tr>
<td>Papillary conjunctivitis</td>
<td>Inflammation of the conjunctiva; nodules and papillae with red tops develop</td>
<td>Environmental irritants; allergens</td>
</tr>
</tbody>
</table>

Table 21.2

**Check Your Understanding**

- How does the lacrimal apparatus help to prevent eye infections?

## 21.2 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. and *Streptococcus* 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.

In this section, we will examine some of the most important bacterial infections of the skin and eyes and discuss how biofilms can contribute to and exacerbate such infections. Key features of bacterial skin and eye infections are also summarized in the Disease Profile boxes throughout this section.
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 healthcare 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 test is 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 21.9).
Figure 21.9  (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)

**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 pimplles 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 21.10**). 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 21.10**). 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 21.10](http://example.com/image1.png)  ![Figure 21.10](http://example.com/image2.png)

Figure 21.10  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 21.11**). 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.
Impetigo

The skin infection impetigo causes the formation of vesicles, pustules, and possibly bullae, often around the nose and mouth. Bullae are large, fluid-filled blisters that measure at least 5 mm in diameter. Impetigo can be diagnosed as either nonbullous or bullous. In nonbullous impetigo, vesicles and pustules rupture and become encrusted sores. Typically the crust is yellowish, often with exudate draining from the base of the lesion. In bullous impetigo, the bullae fill and rupture, resulting in larger, draining, encrusted lesions (Figure 21.12).

Especially common in children, impetigo is particularly concerning because it is highly contagious. Impetigo can be caused by *S. aureus* alone, by *Streptococcus pyogenes* alone, or by coinfection of *S. aureus* and *S. pyogenes*. Impetigo is often diagnosed through observation of its characteristic appearance, although culture and susceptibility testing may also be used.

Topical or oral antibiotic treatment is typically effective in treating most cases of impetigo. However, cases caused by *S. pyogenes* can lead to serious sequelae (pathological conditions resulting from infection, disease, injury, therapy, or other trauma) such as acute glomerulonephritis (AGN), which is severe inflammation in the kidneys.

Nosocomial *S. epidermidis* Infections

Though not as virulent as *S. aureus*, the staphylococcus *S. epidermidis* can cause serious opportunistic infections. Such infections usually occur only in hospital settings. *S. epidermidis* is usually a harmless resident of the normal
skin microbiota. However, health-care workers can inadvertently transfer *S. epidermidis* to medical devices that are inserted into the body, such as catheters, prostheses, and indwelling medical devices. Once it has bypassed the skin barrier, *S. epidermidis* can cause infections inside the body that can be difficult to treat. Like *S. aureus*, *S. epidermidis* is resistant to many antibiotics, and localized infections can become systemic if not treated quickly. To reduce the risk of nosocomial (hospital-acquired) *S. epidermidis*, health-care workers must follow strict procedures for handling and sterilizing medical devices before and during surgical procedures.

**Check Your Understanding**

- Why are *Staphylococcus aureus* infections often purulent?

### Streptococcal Infections of the Skin

*Streptococcus* are gram-positive cocci with a microscopic morphology that resembles chains of bacteria. Colonies are typically small (1–2 mm in diameter), translucent, entire edge, with a slightly raised elevation that can be either nonhemolytic, alpha-hemolytic, or beta-hemolytic when grown on blood agar (Figure 21.13). Additionally, they are facultative anaerobes that are catalase-negative.

![Figure 21.13 Streptococcus pyogenes forms chains of cocci. (credit: modification of work by Centers for Disease Control and Prevention)](image)

The genus *Streptococcus* includes important pathogens that are categorized in serological Lancefield groups based on the distinguishing characteristics of their surface carbohydrates. The most clinically important streptococcal species in humans is *S. pyogenes*, also known as group A streptococcus (GAS). *S. pyogenes* produces a variety of extracellular enzymes, including streptolysins O and S, hyaluronidase, and streptokinase. These enzymes can aid in transmission and contribute to the inflammatory response. *S. pyogenes* also produces a capsule and **M** protein, a streptococcal cell wall protein. These virulence factors help the bacteria to avoid phagocytosis while provoking a substantial immune response that contributes to symptoms associated with streptococcal infections.

*S. pyogenes* causes a wide variety of diseases not only in the skin, but in other organ systems as well. Examples of diseases elsewhere in the body include pharyngitis and scarlet fever, which will be covered in later chapters.

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Cellulitis, Erysipelas, and Erythema Nosodum

Common streptococcal conditions of the skin include cellulitis, erysipelas, and erythema nodosum. An infection that develops in the dermis or hypodermis can cause cellulitis, which presents as a reddened area of the skin that is warm to the touch and painful. The causative agent is often *S. pyogenes*, which may breach the epidermis through a cut or abrasion, although cellulitis may also be caused by staphylococci. *S. pyogenes* can also cause erysipelas, a condition that presents as a large, intensely inflamed patch of skin involving the dermis (often on the legs or face). These infections can be suppurative, which results in a bullous form of erysipelas. Streptococcal and other pathogens may also cause a condition called erythema nodosum, characterized by inflammation in the subcutaneous fat cells of the hypodermis. It sometimes results from a streptococcal infection, though other pathogens can also cause the condition. It is not suppurative, but leads to red nodules on the skin, most frequently on the shins (Figure 21.14).

In general, streptococcal infections are best treated through identification of the specific pathogen followed by treatment based upon that particular pathogen’s susceptibility to different antibiotics. Many immunological tests, including agglutination reactions and ELISAs, can be used to detect streptococci. Penicillin is commonly prescribed for treatment of cellulitis and erysipelas because resistance is not widespread in streptococci at this time. In most patients, erythema nodosum is self-limiting and is not treated with antimicrobial drugs. Recommended treatments may include nonsteroidal anti-inflammatory drugs (NSAIDs), cool wet compresses, elevation, and bed rest.

![Figure 21.14](image1.png)

**Figure 21.14**  *S. pyogenes* can cause a variety of skin conditions once it breaches the skin barrier through a cut or wound. (a) Cellulitis presents as a painful, red rash. (b) Erysipelas presents as a raised rash, usually with clear borders. (c) Erythema nodosum is characterized by red lumps or nodules, typically on the lower legs. (credit a: modification of work by “Bassukas ID, Gaitanis G, Zioga A, Boboyianni C, Stergiopoulou C; credit b: modification of work by Centers for Disease Control and Prevention; credit c: modification of work by Dean C, Crow WT)

Necrotizing Fasciitis

Streptococcal infections that start in the skin can sometimes spread elsewhere, resulting in a rare but potentially life-threatening condition called necrotizing fasciitis, sometimes referred to as flesh-eating bacterial syndrome. *S. pyogenes* is one of several species that can cause this rare but potentially-fatal condition; others include *Klebsiella*, *Clostridium*, *Escherichia coli*, *S. aureus*, and *Aeromonas hydrophila*.

Necrotizing fasciitis occurs when the fascia, a thin layer of connective tissue between the skin and muscle, becomes infected. Severe invasive necrotizing fasciitis due to *Streptococcus pyogenes* occurs when virulence factors that are responsible for adhesion and invasion overcome host defenses. *S. pyogenes* invasins allow bacterial cells to adhere to tissues and establish infection. Bacterial proteases unique to *S. pyogenes* aggressively infiltrate and destroy host tissues, inactivate complement, and prevent neutrophil migration to the site of infection. The infection and resulting tissue death can spread very rapidly, as large areas of skin become detached and die. Treatment generally requires debridement (surgical removal of dead or infected tissue) or amputation of infected limbs to stop the spread of the infection; surgical treatment is supplemented with intravenous antibiotics and other therapies (Figure 21.15).

Necrotizing fasciitis does not always originate from a skin infection; in some cases there is no known portal of entry. Some studies have suggested that experiencing a blunt force trauma can increase the risk of developing streptococcal necrotizing fasciitis. [7]
Figure 21.15  (a) The left leg of this patient shows the clinical features of necrotizing fasciitis. (b) The same patient’s leg is surgically debrided to remove the infection. (credit a, b: modification of work by Piotr Smuszkiewicz, Iwona Trojanowska, and Hanna Tomczak)

Check Your Understanding

- How do staphylococcal infections differ in general presentation from streptococcal infections?

Clinical Focus

Part 2

Observing that Sam's wound is purulent, the doctor tells him that he probably has a bacterial infection. She takes a sample from the lesion to send for laboratory analysis, but because it is Friday, she does not expect to receive the results until the following Monday. In the meantime, she prescribes an over-the-counter topical antibiotic ointment. She tells Sam to keep the wound clean and apply a new bandage with the ointment at least twice per day.

- How would the lab technician determine if the infection is staphylococcal or streptococcal? Suggest several specific methods.
- What tests might the lab perform to determine the best course of antibiotic treatment?

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

Pseudomonas Infections of the Skin

Another important skin pathogen is *Pseudomonas aeruginosa*, a gram-negative, oxidase-positive, aerobic bacillus that is commonly found in water and soil as well as on human skin. *P. aeruginosa* is a common cause of opportunistic infections of wounds and burns. It can also cause hot tub rash, a condition characterized by folliculitis that frequently afflicts users of pools and hot tubs (recall the Clinical Focus case in Microbial Biochemistry). *P. aeruginosa* is also the cause of *otitis externa* (swimmer’s ear), an infection of the ear canal that causes itching, redness, and discomfort, and can progress to fever, pain, and swelling (Figure 21.16).

Figure 21.16  (a) Hot tub folliculitis presents as an itchy red rash. It is typically caused by *P. aeruginosa*, a bacterium that thrives in wet, warm environments such as hot tubs. (b) Otitis externa (swimmer’s ear) may also be caused by *P. aeruginosa* or other bacteria commonly found in water. Inflammation of the outer ear and ear canal can lead to painful swelling. (credit b: modification of work by Klaus D. Peter)

Wounds infected with *P. aeruginosa* have a distinctive odor resembling grape soda or fresh corn tortillas. This odor is caused by the 2-aminoacetophenone that is used by *P. aeruginosa* in quorum sensing and contributes to its pathogenicity. Wounds infected with certain strains of *P. aeruginosa* also produce a blue-green pus due to the pigments pyocyanin and pyoverdin, which also contribute to its virulence. Pyocyanin and pyoverdin are siderophores that help *P. aeruginosa* survive in low-iron environments by enhancing iron uptake. *P. aeruginosa* also produces several other virulence factors, including phospholipase C (a hemolysin capable of breaking down red blood cells), exoenzyme S (involved in adherence to epithelial cells), and exotoxin A (capable of causing tissue necrosis). Other virulence factors include a slime that allows the bacterium to avoid being phagocytized, fimbriae for adherence, and proteases that cause tissue damage. *P. aeruginosa* can be detected through the use of cetrimide agar, which is selective for *Pseudomonas* species (Figure 21.17).

Figure 21.17  (a) These *P. aeruginosa* colonies are growing on xylose lysine sodium deoxycholate (XLD) agar. (b) *Pseudomonas* spp. can produce a variety of blue-green pigments. (c) *Pseudomonas* spp. may produce fluorescein, which fluoresces green under ultraviolet light under the right conditions. (credit a: modification of work by Centers for Disease Control and Prevention)

*Pseudomonas* spp. tend to be resistant to most antibiotics. They often produce β-lactamases, may have mutations affecting porins (small cell wall channels) that affect antibiotic uptake, and may pump some antibiotics out of the cell, contributing to this resistance. Polymyxin B and gentamicin are effective, as are some fluoroquinolones. Otitis externa is typically treated with ear drops containing acetic acid, antibacterials, and/or steroids to reduce inflammation; ear drops may also include antifungals because fungi can sometimes cause or contribute to otitis externa. Wound
infections caused by *Pseudomonas* spp. may be treated with topical antibiofilm agents that disrupt the formation of biofilms.

**Check Your Understanding**

- Name at least two types of skin infections commonly caused by *Pseudomonas* spp.

### Acne

One of the most ubiquitous skin conditions is **acne**. Acne afflicts nearly 80% of teenagers and young adults, but it can be found in individuals of all ages. Higher incidence among adolescents is due to hormonal changes that can result in overproduction of sebum.

Acne occurs when hair follicles become clogged by shed skin cells and sebum, causing non-inflammatory lesions called comedones. Comedones (singular “comedo”) can take the form of whitehead and blackhead pimples. Whiteheads are covered by skin, whereas blackhead pimples are not; the black color occurs when lipids in the clogged follicle become exposed to the air and oxidize (*Figure 21.18*).

![Figure 21.18](a) Acne is characterized by whitehead and blackhead comedones that result from clogged hair follicles. (b) Blackheads, visible as black spots on the skin, have a dark appearance due to the oxidation of lipids in sebum via exposure to the air. (credit a: modification of work by Bruce Blaus)

Often comedones lead to infection by *Propionibacterium acnes*, a gram-positive, non-spore-forming, aerotolerant anaerobic bacillus found on skin that consumes components of sebum. *P. acnes* secretes enzymes that damage the hair follicle, causing inflammatory lesions that may include papules, pustules, nodules, or pseudocysts, depending on their size and severity.

Treatment of acne depends on the severity of the case. There are multiple ways to grade acne severity, but three levels are usually considered based on the number of comedones, the number of inflammatory lesions, and the types of lesions. Mild acne is treated with topical agents that may include salicylic acid (which helps to remove old skin cells) or retinoids (which have multiple mechanisms, including the reduction of inflammation). Moderate acne may be treated with antibiotics (erythromycin, clindamycin), acne creams (e.g., benzoyl peroxide), and hormones. Severe acne may require treatment using strong medications such as isotretinoin (a retinoid that reduces oil buildup, among other effects, but that also has serious side effects such as photosensitivity). Other treatments, such as phototherapy and laser therapy to kill bacteria and possibly reduce oil production, are also sometimes used.
What is the role of *Propionibacterium acnes* in causing acne?

**Resolution**

Sam uses the topical antibiotic over the weekend to treat his wound, but he does not see any improvement. On Monday, the doctor calls to inform him that the results from his laboratory tests are in. The tests show evidence of both *Staphylococcus* and *Streptococcus* in his wound. The bacterial species were confirmed using several tests. A passive agglutination test confirmed the presence of *S. aureus*. In this type of test, latex beads with antibodies cause agglutination when *S. aureus* is present. *Streptococcus pyogenes* was confirmed in the wound based on bacitracin (0.04 units) susceptibility as well as latex agglutination tests specific for *S. pyogenes*.

Because many strains of *S. aureus* are resistant to antibiotics, the doctor had also requested an antimicrobial susceptibility test (AST) at the same time the specimen was submitted for identification. The results of the AST indicated no drug resistance for the *Streptococcus* spp.; the *Staphylococcus* spp. showed resistance to several common antibiotics, but were susceptible to cefoxitin and oxacillin. Once Sam began to use these new antibiotics, the infection resolved within a week and the lesion healed.

Go back to the previous Clinical Focus box.

**Anthrax**

The zoonotic disease anthrax is caused by *Bacillus anthracis*, a gram-positive, endospore-forming, facultative anaerobe. Anthrax mainly affects animals such as sheep, goats, cattle, and deer, but can be found in humans as well. Sometimes called wool sorter’s disease, it is often transmitted to humans through contact with infected animals or animal products, such as wool or hides. However, exposure to *B. anthracis* can occur by other means, as the endospores are widespread in soils and can survive for long periods of time, sometimes for hundreds of years.

The vast majority of anthrax cases (95–99%) occur when anthrax endospores enter the body through abrasions of the skin.[8] This form of the disease is called cutaneous anthrax. It is characterized by the formation of a nodule on the skin; the cells within the nodule die, forming a black eschar, a mass of dead skin tissue (Figure 21.19). The localized infection can eventually lead to bacteremia and septicemia. If untreated, cutaneous anthrax can cause death in 20% of patients.[9] Once in the skin tissues, *B. anthracis* endospores germinate and produce a capsule, which prevents the bacteria from being phagocytized, and two binary exotoxins that cause edema and tissue damage. The first of the two exotoxins consists of a combination of protective antigen (PA) and an enzymatic lethal factor (LF), forming lethal toxin (LeTX). The second consists of protective antigen (PA) and an edema factor (EF), forming edema toxin (EdTX).

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Cutaneous anthrax is an infection of the skin by *B. anthracis*, which produces tissue-damaging exotoxins. Dead tissues accumulating in this nodule have produced a small black eschar. (credit a, b: modification of work by Centers for Disease Control and Prevention)

Less commonly, anthrax infections can be initiated through other portals of entry such as the digestive tract (gastrointestinal anthrax) or respiratory tract (pulmonary anthrax or inhalation anthrax). Typically, cases of noncutaneous anthrax are more difficult to treat than the cutaneous form. The mortality rate for gastrointestinal anthrax can be up to 40%, even with treatment. Inhalation anthrax, which occurs when anthrax spores are inhaled, initially causes influenza-like symptoms, but mortality rates are approximately 45% in treated individuals and 85% in those not treated. A relatively new form of the disease, injection anthrax, has been reported in Europe in intravenous drug users; it occurs when drugs are contaminated with *B. anthracis*. Patients with injection anthrax show signs and symptoms of severe soft tissue infection that differ clinically from cutaneous anthrax. This often delays diagnosis and treatment, and leads to a high mortality rate.\(^\text{[10]}\)

*B. anthracis* colonies on blood agar have a rough texture and serrated edges that eventually form an undulating band (Figure 21.19). Broad spectrum antibiotics such as penicillin, erythromycin, and tetracycline are often effective treatments.\(^\text{[11]}\)

Unfortunately, *B. anthracis* has been used as a biological weapon and remains on the United Nations’ list of potential agents of bioterrorism.\(^\text{[11]}\) Over a period of several months in 2001, a number of letters were mailed to members of the news media and the United States Congress. As a result, 11 individuals developed cutaneous anthrax and another 11 developed inhalation anthrax. Those infected included recipients of the letters, postal workers, and two other individuals. Five of those infected with pulmonary anthrax died. The anthrax spores had been carefully prepared to aerosolize, showing that the perpetrator had a high level of expertise in microbiology.\(^\text{[12]}\)

A vaccine is available to protect individuals from anthrax. However, unlike most routine vaccines, the current anthrax vaccine is unique in both its formulation and the protocols dictating who receives it.\(^\text{[13]}\) The vaccine is administered through five intramuscular injections over a period of 18 months, followed by annual boosters. The US Food and Drug Administration (FDA) has only approved administration of the vaccine prior to exposure for at-risk adults, such as individuals who work with anthrax in a laboratory, some individuals who handle animals or animal products (e.g., some veterinarians), and some members of the United States military. The vaccine protects against cutaneous and

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inhalation anthrax using cell-free filtrates of microaerophilic cultures of an avirulent, nonencapsulated strain of *B. anthracis*. The FDA has not approved the vaccine for routine use after exposure to anthrax, but if there were ever an anthrax emergency in the United States, patients could be given anthrax vaccine after exposure to help prevent disease.

**Check Your Understanding**

- What is the characteristic feature of a cutaneous anthrax infection?

**Disease Profile**

**Bacterial Infections of the Skin**

Bacterial infections of the skin can cause a wide range of symptoms and syndromes, ranging from the superficial and relatively harmless to the severe and even fatal. Most bacterial skin infections can be diagnosed by culturing the bacteria and treated with antibiotics. Antimicrobial susceptibility testing is also often necessary because many strains of bacteria have developed antibiotic resistance. Figure 21.20 summarizes the characteristics of some common bacterial skin infections.

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Bacterial Conjunctivitis

Like the skin, the surface of the eye comes in contact with the outside world and is somewhat prone to infection by bacteria in the environment. Bacterial conjunctivitis (pinkeye) is a condition characterized by inflammation of the conjunctiva, often accompanied by a discharge of sticky fluid (described as acute purulent conjunctivitis) (Figure 21.21). Conjunctivitis can affect one eye or both, and it usually does not affect vision permanently. Bacterial conjunctivitis is most commonly caused by Haemophilus influenzae, but can also be caused by other species such as Moraxella catarrhalis, S. pneumoniae, and S. aureus. The causative agent may be identified using bacterial cultures, Gram stain, and diagnostic biochemical, antigenic, or nucleic acid profile tests of the isolated pathogen. Bacterial conjunctivitis is very contagious, being transmitted via secretions from infected individuals, but it is also self-limiting.
Bacterial conjunctivitis usually resolves in a few days, but topical antibiotics are sometimes prescribed. Because this condition is so contagious, medical attention is recommended whenever it is suspected. Individuals who use contact lenses should discontinue their use when conjunctivitis is suspected. Certain symptoms, such as blurred vision, eye pain, and light sensitivity, can be associated with serious conditions and require medical attention.

**Figure 21.21**  Acute, purulent, bacterial conjunctivitis causes swelling and redness in the conjunctiva, the membrane lining the whites of the eyes and the inner eyelids. It is often accompanied by a yellow, green, or white discharge, which can dry and become encrusted on the eyelashes. (credit: “Tanalai”/Wikimedia Commons)

**Neonatal Conjunctivitis**

Newborns whose mothers have certain sexually transmitted infections are at risk of contracting ophthalmia neonatorum or inclusion conjunctivitis, which are two forms of neonatal conjunctivitis contracted through exposure to pathogens during passage through the birth canal. Gonococcal ophthalmia neonatorum is caused by *Neisseria gonorrhoeae*, the bacterium that causes the STD gonorrhea (Figure 21.22). Inclusion (chlamydial) conjunctivitis is caused by *Chlamydia trachomatis*, the anaerobic, obligate, intracellular parasite that causes the STD chlamydia.

To prevent gonococcal ophthalmia neonatorum, silver nitrate ointments were once routinely applied to all infants’ eyes shortly after birth; however, it is now more common to apply antibacterial creams or drops, such as erythromycin. Most hospitals are required by law to provide this preventative treatment to all infants, because conjunctivitis caused by *N. gonorrhoeae, C. trachomatis*, or other bacteria acquired during a vaginal delivery can have serious complications. If untreated, the infection can spread to the cornea, resulting in ulceration or perforation that can cause vision loss or even permanent blindness. As such, neonatal conjunctivitis is treated aggressively with oral or intravenous antibiotics to stop the spread of the infection. Causative agents of inclusion conjunctivitis may be identified using bacterial cultures, Gram stain, and diagnostic biochemical, antigenic, or nucleic acid profile tests.

**Figure 21.22**  A newborn suffering from gonococcal ophthalmia neonatorum. Left untreated, purulent discharge can scar the cornea, causing loss of vision or permanent blindness. (credit: Centers for Disease Control and Prevention)

*Check Your Understanding*

- Compare and contrast bacterial conjunctivitis with neonatal conjunctivitis.
**Trachoma**

Trachoma, or granular conjunctivitis, is a common cause of preventable blindness that is rare in the United States but widespread in developing countries, especially in Africa and Asia. The condition is caused by the same species that causes neonatal inclusion conjunctivitis in infants, *Chlamydia trachomatis*. *C. trachomatis* can be transmitted easily through fomites such as contaminated towels, bed linens, and clothing and also by direct contact with infected individuals. *C. trachomatis* can also be spread by flies that transfer infected mucous containing *C. trachomatis* from one human to another.

Infection by *C. trachomatis* causes chronic conjunctivitis, which leads to the formation of necrotic follicles and scarring in the upper eyelid. The scars turn the eyelashes inward (a condition known as trichiasis) and mechanical abrasion of the cornea leads to blindness (Figure 21.23). Antibiotics such as azithromycin are effective in treating trachoma, and outcomes are good when the disease is treated promptly. In areas where this disease is common, large public health efforts are focused on reducing transmission by teaching people how to avoid the risks of the infection.

![Figure 21.23](image)

(a) If trachoma is not treated early with antibiotics, scarring on the eyelid can lead to trichiasis, a condition in which the eyelashes turn inward. (b) Trichiasis leads to blindness if not corrected by surgery, as shown here. (credit b: modification of work by Otis Historical Archives National Museum of Health & Medicine)

**Check Your Understanding**

- Why is trachoma rare in the United States?

**SAFE Eradication of Trachoma**

Though uncommon in the United States and other developed nations, trachoma is the leading cause of preventable blindness worldwide, with more than 4 million people at immediate risk of blindness from trichiasis. The vast majority of those affected by trachoma live in Africa and the Middle East in isolated rural or desert communities with limited access to clean water and sanitation. These conditions provide an environment...
conducive to the growth and spread of *Chlamydia trachomatis*, the bacterium that causes trachoma, via wastewater and eye-seeking flies.

In response to this crisis, recent years have seen major public health efforts aimed at treating and preventing trachoma. The Alliance for Global Elimination of Trachoma by 2020 (GET 2020), coordinated by the World Health Organization (WHO), promotes an initiative dubbed “SAFE,” which stands for “Surgery, Antibiotics, Facial cleanliness, and Environmental improvement.” The Carter Center, a charitable, nongovernment organization led by former US President Jimmy Carter, has partnered with the WHO to promote the SAFE initiative in six of the most critically impacted nations in Africa. Through its Trachoma Control Program, the Carter Center trains and equips local surgeons to correct trichiasis and distributes antibiotics to treat trachoma. The program also promotes better personal hygiene through health education and improves sanitation by funding the construction of household latrines. This reduces the prevalence of open sewage, which provides breeding grounds for the flies that spread trachoma.

**Bacterial Keratitis**

Keratitis can have many causes, but bacterial keratitis is most frequently caused by *Staphylococcus epidermidis* and/or *Pseudomonas aeruginosa*. Contact lens users are particularly at risk for such an infection because *S. epidermidis* and *P. aeruginosa* both adhere well to the surface of the lenses. Risk of infection can be greatly reduced by proper care of contact lenses and avoiding wearing lenses overnight. Because the infection can quickly lead to blindness, prompt and aggressive treatment with antibiotics is important. The causative agent may be identified using bacterial cultures, Gram stain, and diagnostic biochemical, antigenic, or nucleic acid profile tests of the isolated pathogen.

**Check Your Understanding**

- Why are contact lens wearers at greater risk for developing keratitis?

**Biofilms and Infections of the Skin and Eyes**

When treating bacterial infections of the skin and eyes, it is important to consider that few such infections can be attributed to a single pathogen. While biofilms may develop in other parts of the body, they are especially relevant to skin infections (such as those caused by *S. aureus* or *P. aeruginosa*) because of their prevalence in chronic skin wounds. Biofilms develop when bacteria (and sometimes fungi) attach to a surface and produce extracellular polymeric substances (EPS) in which cells of multiple organisms may be embedded. When a biofilm develops on a wound, it may interfere with the natural healing process as well as diagnosis and treatment.

Because biofilms vary in composition and are difficult to replicate in the lab, they are still not thoroughly understood. The extracellular matrix of a biofilm consists of polymers such as polysaccharides, extracellular DNA, proteins, and lipids, but the exact makeup varies. The organisms living within the extracellular matrix may include familiar pathogens as well as other bacteria that do not grow well in cultures (such as numerous obligate anaerobes). This presents challenges when culturing samples from infections that involve a biofilm. Because only some species grow *in vitro*, the culture may contain only a subset of the bacterial species involved in the infection.

Biofilms confer many advantages to the resident bacteria. For example, biofilms can facilitate attachment to surfaces on or in the host organism (such as wounds), inhibit phagocytosis, prevent the invasion of neutrophils, and sequester host antibodies. Additionally, biofilms can provide a level of antibiotic resistance not found in the isolated cells and colonies that are typical of laboratory cultures. The extracellular matrix provides a physical barrier to antibiotics, shielding the target cells from exposure. Moreover, cells within a biofilm may differentiate to create subpopulations of dormant cells called persister cells. Nutrient limitations deep within a biofilm add another level of resistance, as stress responses can slow metabolism and increase drug resistance.
Bacterial Infections of the Eyes

A number of bacteria are able to cause infection when introduced to the mucosa of the eye. In general, bacterial eye infections can lead to inflammation, irritation, and discharge, but they vary in severity. Some are typically short-lived, and others can become chronic and lead to permanent eye damage. Prevention requires limiting exposure to contagious pathogens. When infections do occur, prompt treatment with antibiotics can often limit or prevent permanent damage. Figure 21.24 summarizes the characteristics of some common bacterial infections of the eyes.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Pathogen</th>
<th>Signs and Symptoms</th>
<th>Transmission</th>
<th>Antimicrobial Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute bacterial conjunctivitis</td>
<td><em>Haemophilus influenzae</em></td>
<td>Inflammation of conjunctiva, purulent discharge</td>
<td>Exposure to secretions from infected individuals</td>
<td>Broad-spectrum topical antibiotics</td>
</tr>
<tr>
<td>Bacterial keratitis</td>
<td><em>Staphylococcus epidermidis, Pseudomonas aeruginosa</em></td>
<td>Redness and irritation of eye, blurred vision, sensitivity to light; progressive corneal scarring, which can lead to blindness</td>
<td>Exposure to pathogens on contaminated contact lenses</td>
<td>Antibiotic eye drops (e.g., with fluoroquinolones)</td>
</tr>
<tr>
<td>Neonatal conjunctivitis</td>
<td><em>Chlamydia trachomatis, Neisseria gonorrhoeae</em></td>
<td>Inflammation of conjunctiva, purulent discharge, scarring and perforation of cornea; may lead to blindness</td>
<td>Neonate exposed to pathogens in birth canal of mother with chlamydia or gonorrhea</td>
<td>Erythromycin</td>
</tr>
<tr>
<td>Trachoma (granular conjunctivitis)</td>
<td><em>C. trachomatis</em></td>
<td>Chronic conjunctivitis, trichiasis, scarring, blindness</td>
<td>Contact with infected individuals or contaminated fomites; transmission by eye-seeking flies</td>
<td>Azithromycin</td>
</tr>
</tbody>
</table>

Figure 21.24

21.3 Viral Infections of the Skin and Eyes

Learning Objectives

- Identify the most common viruses associated with infections of the skin and eyes
- Compare the major characteristics of specific viral diseases affecting the skin and eyes

Until recently, it was thought that the normal microbiota of the body consisted primarily of bacteria and some fungi. However, in addition to bacteria, the skin is colonized by viruses, and recent studies suggest that Papillomaviridae, Polyomaviridae and Circoviridae also contribute to the normal skin microbiota. However, some viruses associated with skin are pathogenic, and these viruses can cause diseases with a wide variety of presentations.

Numerous types of viral infections cause rashes or lesions on the skin; however, in many cases these skin conditions result from infections that originate in other body systems. In this chapter, we will limit the discussion to viral skin
infections that use the skin as a portal of entry. Later chapters will discuss viral infections such as chickenpox, measles, and rubella—diseases that cause skin rashes but invade the body through portals of entry other than the skin.

**Papillomas**

Papillomas (warts) are the expression of common skin infections by human papillomavirus (HPV) and are transmitted by direct contact. There are many types of HPV, and they lead to a variety of different presentations, such as common warts, plantar warts, flat warts, and filiform warts. HPV can also cause sexually-transmitted genital warts, which will be discussed in *Urogenital System Infections*. Vaccination is available for some strains of HPV.

Common warts tend to develop on fingers, the backs of hands, and around nails in areas with broken skin. In contrast, plantar warts (also called foot warts) develop on the sole of the foot and can grow inwards, causing pain and pressure during walking. Flat warts can develop anywhere on the body, are often numerous, and are relatively smooth and small compared with other wart types. Filiform warts are long, threadlike warts that grow quickly.

In some cases, the immune system may be strong enough to prevent warts from forming or to eradicate established warts. However, treatment of established warts is typically required. There are many available treatments for warts, and their effectiveness varies. Common warts can be frozen off with liquid nitrogen. Topical applications of salicylic acid may also be effective. Other options are electrosurgery (burning), curettage (cutting), excision, painting with cantharidin (which causes the wart to die so it can more easily be removed), laser treatments, treatment with bleomycin, chemical peels, and immunotherapy (Figure 21.25).

![Figure 21.25](image)

**Oral Herpes**

Another common skin virus is herpes simplex virus (HSV). HSV has historically been divided into two types, HSV-1 and HSV-2. HSV-1 is typically transmitted by direct oral contact between individuals, and is usually associated with oral herpes. HSV-2 is usually transmitted sexually and is typically associated with genital herpes. However, both HSV-1 and HSV-2 are capable of infecting any mucous membrane, and the incidence of genital HSV-1 and oral HSV-2 infections has been increasing in recent years. In this chapter, we will limit our discussion to infections caused by HSV-1; HSV-2 and genital herpes will be discussed in *Urogenital System Infections*.

Infection by HSV-1 commonly manifests as cold sores or fever blisters, usually on or around the lips (Figure 21.26). HSV-1 is highly contagious, with some studies suggesting that up to 65% of the US population is infected; however, many infected individuals are asymptomatic. Moreover, the virus can be latent for long periods, residing in the trigeminal nerve ganglia between recurring bouts of symptoms. Recurrence can be triggered by stress or
environmental conditions (systemic or affecting the skin). When lesions are present, they may blister, break open, and crust. The virus can be spread through direct contact, even when a patient is asymptomatic.

While the lips, mouth, and face are the most common sites for HSV-1 infections, lesions can spread to other areas of the body. Wrestlers and other athletes involved in contact sports may develop lesions on the neck, shoulders, and trunk. This condition is often called herpes gladiatorum. Herpes lesions that develop on the fingers are often called herpetic whitlow.

HSV-1 infections are commonly diagnosed from their appearance, although laboratory testing can confirm the diagnosis. There is no cure, but antiviral medications such as acyclovir, penciclovir, famciclovir, and valacyclovir are used to reduce symptoms and risk of transmission. Topical medications, such as creams with n-docosanol and penciclovir, can also be used to reduce symptoms such as itching, burning, and tingling.

![Figure 21.26](credit: Centers for Disease Control and Prevention)

**Figure 21.26** This cold sore was caused by HSV-1. (credit: Centers for Disease Control and Prevention)

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**Check Your Understanding**

- What are the most common sites for the appearance of herpetic lesions?

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**Roseola and Fifth Disease**

The viral diseases **roseola** and **fifth disease** are somewhat similar in terms of their presentation, but they are caused by different viruses. Roseola, sometimes called roseola infantum or exanthem subitum (“sudden rash”), is a mild viral infection usually caused by human herpesvirus-6 (HHV-6) and occasionally by HHV-7. It is spread via direct contact with the saliva or respiratory secretions of an infected individual, often through droplet aerosols. Roseola is very common in children, with symptoms including a runny nose, a sore throat, and a cough, along with (or followed by) a high fever (39.4 °C). About three to five days after the fever subsides, a rash may begin to appear on the chest and abdomen. The rash, which does not cause discomfort, initially forms characteristic macules that are flat or papules that are firm and slightly raised; some macules or papules may be surrounded by a white ring. The rash may eventually spread to the neck and arms, and sometimes continues to spread to the face and legs. The diagnosis is generally made based upon observation of the symptoms. However, it is possible to perform serological tests to confirm the diagnosis. While treatment may be recommended to control the fever, the disease usually resolves without treatment within a week after the fever develops. For individuals at particular risk, such as those who are immunocompromised, the antiviral medication ganciclovir may be used.

Fifth disease (also known as erythema infectiosum) is another common, highly contagious illness that causes a distinct rash that is critical to diagnosis. Fifth disease is caused by parvovirus B19, and is transmitted by contact
with respiratory secretions from an infected individual. Infection is more common in children than adults. While approximately 20% of individuals will be asymptomatic during infection, others will exhibit cold-like symptoms (headache, fever, and upset stomach) during the early stages when the illness is most infectious. Several days later, a distinct red facial rash appears, often called “slapped cheek” rash (Figure 21.27). Within a few days, a second rash may appear on the arms, legs, chest, back, or buttocks. The rash may come and go for several weeks, but usually disappears within seven to twenty-one days, gradually becoming lacy in appearance as it recedes.

In children, the disease usually resolves on its own without medical treatment beyond symptom relief as needed. Adults may experience different and possibly more serious symptoms. Many adults with fifth disease do not develop any rash, but may experience joint pain and swelling that lasts several weeks or months. Immunocompromised individuals can develop severe anemia and may need blood transfusions or immune globulin injections. While the rash is the most important component of diagnosis (especially in children), the symptoms of fifth disease are not always consistent. Serological testing can be conducted for confirmation.

![Figure 21.27](image)

(a) Roseola, a mild viral infection common in young children, generally begins with symptoms similar to a cold, followed by a pink, patchy rash that starts on the trunk and spreads outward. (b) Fifth disease exhibits similar symptoms in children, except for the distinctive “slapped cheek” rash that originates on the face.

Check Your Understanding

- Identify at least one similarity and one difference between roseola and fifth disease.

Viral Conjunctivitis

Like bacterial conjunctivitis viral infections of the eye can cause inflammation of the conjunctiva and discharge from the eye. However, viral conjunctivitis tends to produce a discharge that is more watery than the thick discharge associated with bacterial conjunctivitis. The infection is contagious and can easily spread from one eye to the other or to other individuals through contact with eye discharge.

Viral conjunctivitis is commonly associated with colds caused by adenoviruses; however, other viruses can also cause conjunctivitis. If the causative agent is uncertain, eye discharge can be tested to aid in diagnosis. Antibiotic treatment of viral conjunctivitis is ineffective, and symptoms usually resolve without treatment within a week or two.

**Herpes Keratitis**

Herpes infections caused by HSV-1 can sometimes spread to the eye from other areas of the body, which may result in keratoconjunctivitis. This condition, generally called *herpes keratitis* or herpetic keratitis, affects the conjunctiva and cornea, causing irritation, excess tears, and sensitivity to light. Deep lesions in the cornea may eventually form, leading to blindness. Because keratitis can have numerous causes, laboratory testing is necessary to confirm the diagnosis when HSV-1 is suspected; once confirmed, antiviral medications may be prescribed.

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**Disease Profile**

**Viral Infections of the Skin and Eyes**

A number of viruses can cause infections via direct contact with skin and eyes, causing signs and symptoms ranging from rashes and lesions to warts and conjunctivitis. All of these viral diseases are contagious, and while some are more common in children (fifth disease and roseola), others are prevalent in people of all ages (oral herpes, viral conjunctivitis, papillomas). In general, the best means of prevention is avoiding contact with infected individuals. Treatment may require antiviral medications; however, several of these conditions are mild and typically resolve without treatment. Figure 21.28 summarizes the characteristics of some common viral infections of the skin and eyes.
Learning Objectives

- Identify the most common fungal pathogens associated with cutaneous and subcutaneous mycoses
- Compare the major characteristics of specific fungal diseases affecting the skin

Many fungal infections of the skin involve fungi that are found in the normal skin microbiota. Some of these fungi can cause infection when they gain entry through a wound; others mainly cause opportunistic infections in immunocompromised patients. Other fungal pathogens primarily cause infection in unusually moist environments that promote fungal growth; for example, sweaty shoes, communal showers, and locker rooms provide excellent breeding grounds that promote the growth and transmission of fungal pathogens.

Fungal infections, also called mycoses, can be divided into classes based on their invasiveness. Mycoses that cause superficial infections of the epidermis, hair, and nails, are called cutaneous mycoses. Mycoses that penetrate the epidermis and the dermis to infect deeper tissues are called subcutaneous mycoses. Mycoses that spread throughout the body are called systemic mycoses.
Tineas

A group of cutaneous mycoses called tineas are caused by dermatophytes, fungal molds that require keratin, a protein found in skin, hair, and nails, for growth. There are three genera of dermatophytes, all of which can cause cutaneous mycoses: *Trichophyton*, *Epidermophyton*, and *Microsporum*. Tineas on most areas of the body are generally called ringworm, but tineas in specific locations may have distinctive names and symptoms (see Table 21.3 and Figure 21.29). Keep in mind that these names—even though they are Latinized—refer to locations on the body, not causative organisms. Tineas can be caused by different dermatophytes in most areas of the body.

### Some Common Tineas and Location on the Body

<table>
<thead>
<tr>
<th>Tinea corporis (ringworm)</th>
<th>Body</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tinea capitis (ringworm)</td>
<td>Scalp</td>
</tr>
<tr>
<td>Tinea pedis (athlete’s foot)</td>
<td>Feet</td>
</tr>
<tr>
<td>Tinea barbae (barber’s itch)</td>
<td>Beard</td>
</tr>
<tr>
<td>Tinea cruris (jock itch)</td>
<td>Groin</td>
</tr>
<tr>
<td>Tinea unguium (onychomycosis)</td>
<td>Toenails, fingernails</td>
</tr>
</tbody>
</table>

Table 21.3

![Tinea corporis](image1)

**Figure 21.29** Tineas are superficial cutaneous mycoses and are common. (a) Tinea barbae (barber’s itch) occurs on the lower face. (b) Tinea pedis (athlete’s foot) occurs on the feet, causing itching, burning, and dry, cracked skin between the toes. (c) A close-up view of tinea corporis (ringworm) caused by *Trichophyton mentagrophytes*. (credit a, c: modification of work by Centers for Disease Control and Prevention; credit b: modification of work by Al Hasan M, Fitzgerald SM, Saoudian M, Krishnaswamy G)

Dermatophytes are commonly found in the environment and in soils and are frequently transferred to the skin via contact with other humans and animals. Fungal spores can also spread on hair. Many dermatophytes grow well in moist, dark environments. For example, *tinea pedis* (athlete’s foot) commonly spreads in public showers, and the causative fungi grow well in the dark, moist confines of sweaty shoes and socks. Likewise, *tinea cruris* (jock itch) often spreads in communal living environments and thrives in warm, moist undergarments.

Tineas on the body (*tinea corporis*) often produce lesions that grow radially and heal towards the center. This causes the formation of a red ring, leading to the misleading name of ringworm recall the Clinical Focus case in *The Eukaryotes of Microbiology*.

Several approaches may be used to diagnose tineas. A Wood’s lamp (also called a black lamp) with a wavelength of 365 nm is often used. When directed on a tinea, the ultraviolet light emitted from the Wood’s lamp causes the fungal elements (spores and hyphae) to fluoresce. Direct microscopic evaluation of specimens from skin scrapings, hair, or nails can also be used to detect fungi. Generally, these specimens are prepared in a wet mount using a potassium hydroxide solution (10%–20% aqueous KOH), which dissolves the keratin in hair, nails, and skin cells to
allow for visualization of the hyphae and fungal spores. The specimens may be grown on Sabouraud dextrose CC (chloramphenicol/cyclohexamide), a selective agar that supports dermatophyte growth while inhibiting the growth of bacteria and saprophytic fungi (Figure 21.30). Macroscopic colony morphology is often used to initially identify the genus of the dermatophyte; identification can be further confirmed by visualizing the microscopic morphology using either a slide culture or a sticky tape prep stained with lactophenol cotton blue.

Various antifungal treatments can be effective against tineas. Allylamine ointments that include terbinafine are commonly used; miconazole and clotrimazole are also available for topical treatment, and griseofulvin is used orally.

![Image](image.jpg)

**Figure 21.30** To diagnose tineas, the dermatophytes may be grown on a Sabouraud dextrose CC agar plate. This culture contains a strain of *Trichophyton rubrum*, one of the most common causes of tineas on various parts of the body. (credit: Centers for Disease Control and Prevention)

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**Check Your Understanding**

- Why are tineas, caused by fungal molds, often called ringworm?

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**Cutaneous Aspergillosis**

Another cause of cutaneous mycoses is *Aspergillus*, a genus consisting of molds of many different species, some of which cause a condition called aspergillosis. Primary cutaneous aspergillosis, in which the infection begins in the skin, is rare but does occur. More common is secondary cutaneous aspergillosis, in which the infection begins in the respiratory system and disseminates systemically. Both primary and secondary cutaneous aspergillosis result in distinctive eschars that form at the site or sites of infection (Figure 21.31). Pulmonary aspergillosis will be discussed more thoroughly in *Respiratory Mycoses*.)
Primary cutaneous aspergillosis usually occurs at the site of an injury and is most often caused by *Aspergillus fumigatus* or *Aspergillus flavus*. It is usually reported in patients who have had an injury while working in an agricultural or outdoor environment. However, opportunistic infections can also occur in health-care settings, often at the site of intravenous catheters, venipuncture wounds, or in association with burns, surgical wounds, or occlusive dressing. After candidiasis, aspergillosis is the second most common hospital-acquired fungal infection and often occurs in immunocompromised patients, who are more vulnerable to opportunistic infections.

Cutaneous aspergillosis is diagnosed using patient history, culturing, histopathology using a skin biopsy. Treatment involves the use of antifungal medications such as voriconazole (preferred for invasive aspergillosis), itraconazole, and amphotericin B if itraconazole is not effective. For immunosuppressed individuals or burn patients, medication may be used and surgical or immunotherapy treatments may be needed.

Check Your Understanding

- Identify the sources of infection for primary and secondary cutaneous aspergillosis.

**Candidiasis of the Skin and Nails**

*Candida albicans* and other yeasts in the genus *Candida* can cause skin infections referred to as cutaneous candidiasis. *Candida* spp. are sometimes responsible for intertrigo, a general term for a rash that occurs in a skin fold, or other localized rashes on the skin. *Candida* can also infect the nails, causing them to become yellow and harden (Figure 21.32).
Candidiasis of the skin and nails is diagnosed through clinical observation and through culture, Gram stain, and KOH wet mounts. Susceptibility testing for anti-fungal agents can also be done. Cutaneous candidiasis can be treated with topical or systemic azole antifungal medications. Because candidiasis can become invasive, patients suffering from HIV/AIDS, cancer, or other conditions that compromise the immune system may benefit from preventive treatment. Azoles, such as clotrimazole, econazole, fluconazole, ketoconazole, and miconazole; nystatin; terbinafine; and naftifine may be used for treatment. Long-term treatment with medications such as itraconazole or ketoconazole may be used for chronic infections. Repeat infections often occur, but this risk can be reduced by carefully following treatment recommendations, avoiding excessive moisture, maintaining good health, practicing good hygiene, and having appropriate clothing (including footwear).

*Candida* also causes infections in other parts of the body besides the skin. These include vaginal yeast infections (see *Fungal Infections of the Reproductive System*) and oral thrush (see *Microbial Diseases of the Mouth and Oral Cavity*).

**Check Your Understanding**

- What are the signs and symptoms of candidiasis of the skin and nails?

**Sporotrichosis**

Whereas cutaneous mycoses are superficial, subcutaneous mycoses can spread from the skin to deeper tissues. In temperate regions, the most common subcutaneous mycosis is a condition called *sporotrichosis*, caused by the fungus *Sporothrix schenckii* and commonly known as rose gardener’s disease or rose thorn disease (recall *Case in Point: Every Rose Has Its Thorn*). Sporotrichosis is often contracted after working with soil, plants, or timber, as the fungus can gain entry through a small wound such as a thorn-prick or splinter. Sporotrichosis can generally be avoided by wearing gloves and protective clothing while gardening and promptly cleaning and disinfecting any wounds sustained during outdoor activities.

*Sporothrix* infections initially present as small ulcers in the skin, but the fungus can spread to the lymphatic system and sometimes beyond. When the infection spreads, nodules appear, become necrotic, and may ulcerate. As more lymph nodes become affected, abscesses and ulceration may develop over a larger area (often on one arm or hand). In severe cases, the infection may spread more widely throughout the body, although this is relatively uncommon.
Sporothrix infection can be diagnosed based upon histologic examination of the affected tissue. Its macroscopic morphology can be observed by culturing the mold on potato dextrose agar, and its microscopic morphology can be observed by staining a slide culture with lactophenol cotton blue. Treatment with itraconazole is generally recommended.

**Check Your Understanding**

- Describe the progression of a *Sporothrix schenckii* infection.

**Disease Profile**

**Mycoses of the Skin**

Cutaneous mycoses are typically opportunistic, only able to cause infection when the skin barrier is breached through a wound. Tineas are the exception, as the dermatophytes responsible for tineas are able to grow on skin, hair, and nails, especially in moist conditions. Most mycoses of the skin can be avoided through good hygiene and proper wound care. Treatment requires antifungal medications. **Figure 21.33** summarizes the characteristics of some common fungal infections of the skin.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Pathogen</th>
<th>Signs and Symptoms</th>
<th>Transmission</th>
<th>Antimicrobial Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspergillosis (cutaneous)</td>
<td><em>Aspergillus fumigatus</em>, <em>Aspergillus flavus</em></td>
<td>Distinctive eschars at site(s) of infection</td>
<td>Entry via wound (primary cutaneous aspergillosis) or via the respiratory system (secondary cutaneous aspergillosis); commonly a hospital-acquired infection</td>
<td>Itraconazole, voriconazole, amphotericin B</td>
</tr>
<tr>
<td>Candidiasis (cutaneous)</td>
<td><em>Candida albicans</em></td>
<td>Intertrigo, localized rash, yellowing of nails</td>
<td>Overgrowth of normal skin microbiota, especially in moist, dark areas</td>
<td>Azoles</td>
</tr>
<tr>
<td>Sporotrichosis (rose gardener’s disease)</td>
<td><em>Sporothrix schenckii</em></td>
<td>Subcutaneous ulcers and abscesses; may spread to a large area, e.g., hand or arm</td>
<td>Entry via thorn prick or other wound</td>
<td>Itraconazole</td>
</tr>
<tr>
<td>Tineas</td>
<td><em>Trichophyton spp.</em>, <em>Epidermophyton spp.</em>, <em>Microsporum spp.</em></td>
<td>Itchy, ring-like lesions (ringworm) at sites of infection</td>
<td>Contact with dermatophytic fungi, especially in warm, moist environments conducive to fungal growth</td>
<td>Terbinafine, miconazole, clotrimazole, griseofulvin</td>
</tr>
</tbody>
</table>

**Figure 21.33**
21.5 Protozoan and Helminthic Infections of the Skin and Eyes

Learning Objectives

- Identify two parasites that commonly cause infections of the skin and eyes
- Identify the major characteristics of specific parasitic diseases affecting the skin and eyes

Many parasitic protozoans and helminths use the skin or eyes as a portal of entry. Some may physically burrow into the skin or the mucosa of the eye; others breach the skin barrier by means of an insect bite. Still others take advantage of a wound to bypass the skin barrier and enter the body, much like other opportunistic pathogens. Although many parasites enter the body through the skin, in this chapter we will limit our discussion to those for which the skin or eyes are the primary site of infection. Parasites that enter through the skin but travel to a different site of infection will be covered in other chapters. In addition, we will limit our discussion to microscopic parasitic infections of the skin and eyes. Macroscopic parasites such as lice, scabies, mites, and ticks are beyond the scope of this text.

**Acanthamoeba Infections**

*Acanthamoeba* is a genus of free-living protozoan amoebae that are common in soils and unchlorinated bodies of fresh water. (This is one reason why some swimming pools are treated with chlorine.) The genus contains a few parasitic species, some of which can cause infections of the eyes, skin, and nervous system. Such infections can sometimes travel and affect other body systems. Skin infections may manifest as abscesses, ulcers, and nodules. When acanthamoebae infect the eye, causing inflammation of the cornea, the condition is called *Acanthamoeba keratitis*. Figure 21.34 illustrates the *Acanthamoeba* life cycle and various modes of infection.

While *Acanthamoeba* keratitis is initially mild, it can lead to severe corneal damage, vision impairment, or even blindness if left untreated. Similar to eye infections involving *P. aeruginosa*, *Acanthamoeba* poses a much greater risk to wearers of contact lenses because the amoeba can thrive in the space between contact lenses and the cornea. Prevention through proper contact lens care is important. Lenses should always be properly disinfected prior to use, and should never be worn while swimming or using a hot tub.

*Acanthamoeba* can also enter the body through other pathways, including skin wounds and the respiratory tract. It usually does not cause disease except in immunocompromised individuals; however, in rare cases, the infection can spread to the nervous system, resulting in a usually fatal condition called granulomatous amoebic encephalitis (GAE) (see *Fungal and Parasitic Diseases of the Nervous System*). Disseminated infections, lesions, and *Acanthamoeba* keratitis can be diagnosed by observing symptoms and examining patient samples under the microscope to view the parasite. Skin biopsies may be used.

*Acanthamoeba* keratitis is difficult to treat, and prompt treatment is necessary to prevent the condition from progressing. The condition generally requires three to four weeks of intensive treatment to resolve. Common treatments include topical antiseptics (e.g., polyhexamethylene biguanide, chlorhexidine, or both), sometimes with painkillers or corticosteroids (although the latter are controversial because they suppress the immune system, which can worsen the infection). Azoles are sometimes prescribed as well. Advanced cases of keratitis may require a corneal transplant to prevent blindness.
Acanthamoeba spp. are waterborne parasites very common in unchlorinated aqueous environments. As shown in this life cycle, Acanthamoeba cysts and trophozoites are both capable of entering the body through various routes, causing infections of the eye, skin, and central nervous system. (credit: modification of work by Centers for Disease Control and Prevention)

Acanthamoeba cyst

Acanthamoeba trophozoite

Acanthamoeba keratitis. The fluorescent color, which is due to sodium fluorescein application, highlights significant damage to the cornea and vascularization of the surrounding conjunctiva. (credit a: modification of work by Centers for Disease Control and Prevention; credit b, c: modification of work by Jacob Lorenzo-Morales, Naveed A Kahn and Julia Walochnik)

Check Your Understanding

- How are Acanthamoeba infections acquired?
Loiasis

The helminth *Loa loa*, also known as the African eye worm, is a nematode that can cause loiasis, a disease endemic to West and Central Africa (Figure 21.36). The disease does not occur outside that region except when carried by travelers. There is evidence that individual genetic differences affect susceptibility to developing loiasis after infection by the *Loa loa* worm. Even in areas in which *Loa loa* worms are common, the disease is generally found in less than 30% of the population. It has been suggested that travelers who spend time in the region may be somewhat more susceptible to developing symptoms than the native population, and the presentation of infection may differ.

The parasite is spread by deerflies (genus *Chrysops*), which can ingest the larvae from an infected human via a blood meal (Figure 21.36). When the deerfly bites other humans, it deposits the larvae into their bloodstreams. After about five months in the human body, some larvae develop into adult worms, which can grow to several centimeters in length and live for years in the subcutaneous tissue of the host.

The name “eye worm” alludes to the visible migration of worms across the conjunctiva of the eye. Adult worms live in the subcutaneous tissues and can travel at about 1 cm per hour. They can often be observed when migrating through the eye, and sometimes under the skin; in fact, this is generally how the disease is diagnosed. It is also possible to test for antibodies, but the presence of antibodies does not necessarily indicate a current infection; it only means that the individual was exposed at some time. Some patients are asymptomatic, but in others the migrating worms can cause fever and areas of allergic inflammation known as Calabar swellings. Worms migrating through the conjunctiva can cause temporary eye pain and itching, but generally there is no lasting damage to the eye. Some patients experience a range of other symptoms, such as widespread itching, hives, and joint and muscle pain.

Worms can be surgically removed from the eye or the skin, but this treatment only relieves discomfort; it does not cure the infection, which involves many worms. The preferred treatment is diethylcarbamazine, but this medication produces severe side effects in some individuals, such as brain inflammation and possible death in patients with heavy infections. Albendazole is also sometimes used if diethylcarbamazine is not appropriate or not successful. If left untreated for many years, loiasis can damage the kidneys, heart, and lungs, though these symptoms are rare.

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**Figure 21.36** This *Loa loa* worm, measuring about 55 mm long, was extracted from the conjunctiva of a patient with loiasis. The *Loa loa* has a complex life cycle. Biting deerflies native to the rain forests of Central and West Africa transmit the larvae between humans. (credit a: modification of work by Eballe AO, Epée E, Koki G, Owono D, Mvogo 946 Chapter 21 | Skin and Eye Infections
- Describe the most common way to diagnose loiasis.

See a video (https://openstax.org/l/22microfilvid) of a live Loa loa microfilaria under the microscope.

Parasitic Skin and Eye Infections

The protozoan Acanthamoeba and the helminth Loa loa are two parasites capable of causing infections of the skin and eyes. Figure 21.37 summarizes the characteristics of some common fungal infections of the skin.

<table>
<thead>
<tr>
<th>Parasitic Skin and Eye Infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease</td>
</tr>
<tr>
<td>---------</td>
</tr>
<tr>
<td>Acanthamoeba keratitis</td>
</tr>
<tr>
<td>Loiasis</td>
</tr>
</tbody>
</table>

Figure 21.37

Summary

21.1 Anatomy and Normal Microbiota of the Skin and Eyes

- Human skin consists of two main layers, the epidermis and dermis, which are situated on top of the hypodermis, a layer of connective tissue.
- The skin is an effective physical barrier against microbial invasion.
The skin’s relatively dry environment and normal microbiota discourage colonization by transient microbes. The skin’s normal microbiota varies from one region of the body to another. The conjunctiva of the eye is a frequent site for microbial infection, but deeper eye infections are less common; multiple types of conjunctivitis exist.

### 21.2 Bacterial Infections of the Skin and Eyes

- **Staphylococcus** and **Streptococcus** cause 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 staphylococcal infections are an ongoing problem because many people are asymptomatic carriers.
- **Group A streptococci** (GAS), **S. pyogenes**, is often responsible for cases of cellulitis, erysipelas, and erythema nodosum. GAS are also one of many possible causes of necrotizing fasciitis.
- **P. aeruginosa** is often responsible for infections of the skin and eyes, including wound and burn infections, hot tub rash, otitis externa, and bacterial keratitis.
- **Acne** is a common skin condition that can become more inflammatory when *Propionibacterium acnes* infects hair follicles and pores clogged with dead skin cells and sebum.
- Cutaneous anthrax occurs when *Bacillus anthracis* breaches the skin barrier. The infection results in a localized black eschar on skin. Anthrax can be fatal if *B. anthracis* spreads to the bloodstream.
- Common bacterial conjunctivitis is often caused by *Haemophilus influenzae* and usually resolves on its own in a few days. More serious forms of conjunctivitis include gonococcal ophthalmia neonatorum, inclusion conjunctivitis (chlamydial), and trachoma, all of which can lead to blindness if untreated.
- **Keratitis** is frequently caused by *Staphylococcus epidermidis* and/or *Pseudomonas aeruginosa*, especially among contact lens users, and can lead to blindness.
- Biofilms complicate the treatment of wound and eye infections because pathogens living in biofilms can be difficult to treat and eliminate.

### 21.3 Viral Infections of the Skin and Eyes

- **Papillomas** (warts) are caused by human papillomaviruses.
- **Herpes simplex virus** (especially HSV-1) mainly causes oral herpes, but lesions can appear on other areas of the skin and mucous membranes.
- **Roseola** and fifth disease are common viral illnesses that cause skin rashes; roseola is caused by HHV-6 and HHV-7 while fifth disease is caused by parvovirus 19.
- **Viral conjunctivitis** is often caused by adenoviruses and may be associated with the common cold. Herpes keratitis is caused by herpesviruses that spread to the eye.

### 21.4 Mycoses of the Skin

- **Mycoses** can be cutaneous, subcutaneous, or systemic.
- Common cutaneous mycoses include tineas caused by dermatophytes of the genera *Trichophyton*, *Epidermophyton*, and *Microsporum*. *Tinea corporis* is called ringworm. Tineas on other parts of the body have names associated with the affected body part.
- **Aspergillosis** is a fungal disease caused by molds of the genus *Aspergillus*. Primary cutaneous aspergillosis enters through a break in the skin, such as the site of an injury or a surgical wound; it is a common hospital-acquired infection. In secondary cutaneous aspergillosis, the fungus enters via the respiratory system and disseminates systemically, manifesting in lesions on the skin.
- The most common subcutaneous mycosis is sporotrichosis (rose gardener’s disease), caused by *Sporothrix schenckii*. 
Yeast of the genus *Candida* can cause opportunistic infections of the skin called *candidiasis*, producing *intertrigo*, localized rashes, or yellowing of the nails.

### 21.5 Protozoan and Helminthic Infections of the Skin and Eyes

- The protozoan *Acanthamoeba* and the helminth *Loa loa* are two parasites that can breach the skin barrier, causing infections of the skin and eyes.
- *Acanthamoeba keratitis* is a parasitic infection of the eye that often results from improper disinfection of contact lenses or swimming while wearing contact lenses.
- *Loiasis*, or eye worm, is a disease endemic to Africa that is caused by parasitic worms that infect the subcutaneous tissue of the skin and eyes. It is transmitted by deerfly vectors.

### Review Questions

#### Multiple Choice

1. __________ glands produce a lipid-rich substance that contains proteins and minerals and protects the skin.
   - a. Sweat
   - b. Mammary
   - c. Sebaceous
   - d. Endocrine

2. Which layer of skin contains living cells, is vascularized, and lies directly above the hypodermis?
   - a. the stratum corneum
   - b. the dermis
   - c. the epidermis
   - d. the conjunctiva

3. *Staphylococcus aureus* is most often associated with being
   - a. coagulase-positive.
   - b. coagulase-negative.
   - c. catalase-negative.
   - d. gram-negative

4. M protein is produced by
   - a. *Pseudomonas aeruginosa*
   - b. *Staphylococcus aureus*
   - c. *Propionibacterium acnes*
   - d. *Streptococcus pyogenes*

5. __________ is a major cause of preventable blindness that can be reduced through improved sanitation.
   - a. Ophthalmia neonatorum
   - b. Keratitis
   - c. Trachoma
   - d. Cutaneous anthrax

6. Which species is frequently associated with nosocomial infections transmitted via medical devices inserted into the body?
   - a. *Staphylococcus epidermidis*
   - b. *Streptococcus pyogenes*
   - c. *Propionibacterium acnes*
   - d. *Bacillus anthracis*

7. Warts are caused by
   - a. human papillomavirus.
   - b. herpes simplex virus.
   - c. adenoviruses.
   - d. parvovirus B19.

8. Which of these viruses can spread to the eye to cause a form of keratitis?
   - a. human papillomavirus
   - b. herpes simplex virus 1
   - c. parvovirus 19
   - d. circoviruses

9. Cold sores are associated with:
   - a. human papillomavirus
   - b. roseola
   - c. herpes simplex viruses
   - d. human herpesvirus 6

10. Which disease is usually self-limiting but is most commonly treated with ganciclovir if medical treatment is needed?
    - a. roseola
    - b. oral herpes
    - c. papillomas
    - d. viral conjunctivitis

11. Adenoviruses can cause:
    - a. viral conjunctivitis
    - b. herpetic conjunctivitis
    - c. papillomas
    - d. oral herpes
12. _________ is a superficial fungal infection found on the head.
   a. Tinea cruris
   b. Tinea capitis
   c. Tinea pedis
   d. Tinea corporis

13. For what purpose would a health-care professional use a Wood’s lamp for a suspected case of ringworm?
   a. to prevent the rash from spreading
   b. to kill the fungus
   c. to visualize the fungus
   d. to examine the fungus microscopically

14. Sabouraud dextrose agar CC is selective for:
   a. all fungi
   b. non-saprophytic fungi
   c. bacteria
   d. viruses

15. The first-line recommended treatment for sporotrichosis is:
   a. itraconazole
   b. clindamycin
   c. amphotericin
   d. nystatin

16. Which of the following is most likely to cause an Acanthamoeba infection?
   a. swimming in a lake while wearing contact lenses
   b. being bitten by deerflies in Central Africa
   c. living environments in a college dormitory with communal showers
   d. participating in a contact sport such as wrestling

17. The parasitic Loa loa worm can cause great pain when it:
   a. moves through the bloodstream
   b. exits through the skin of the foot
   c. travels through the conjunctiva
   d. enters the digestive tract

18. A patient tests positive for Loa loa antibodies. What does this test indicate?
   a. The individual was exposed to Loa loa at some point.
   b. The individual is currently suffering from loiasis.
   c. The individual has never been exposed to Loa loa.
   d. The individual is immunosuppressed.

**Fill in the Blank**

20. The ________ is the outermost layer of the epidermis.

21. The mucous membrane that covers the surface of the eyeball and inner eyelid is called the ________.
22. A purulent wound produces _______.
23. Human herpesvirus 6 is the causative agent of _______.
24. The most common subcutaneous mycosis in temperate regions is _______.
25. Eye worm is another name for _______.
26. The _______ is the part of the eye that is damaged due to *Acanthamoeba* keratitis.

**Short Answer**

27. What is the role of keratin in the skin?
28. What are two ways in which tears help to prevent microbial colonization?
29. Which label indicates a sweat gland?

![Figure 21.38](credit: modification of work by National Cancer Institute)

30. How are leukocidins associated with pus production?
31. What is a good first test to distinguish streptococcal infections from staphylococcal infections?
32. Compare and contrast bacterial and viral conjunctivitis.
33. What yeasts commonly cause opportunistic infections?

**Critical Thinking**

34. Explain why it is important to understand the normal microbiota of the skin.
35. Besides the presence or absence of ulceration, how do acute ulcerative and nonulcerative blepharitis differ?
36. What steps might you recommend to a patient for reducing the risk of developing a fungal infection of the toenails?
37. Why might a traveler to a region with *Loa loa* worm have a greater risk of serious infection compared with people who live in the region?
38. What preventative actions might you recommend to a patient traveling to a region where loiasis is endemic?
Chapter 22

Respiratory System Infections

Figure 22.1 Aerosols produced by sneezing, coughing, or even just speaking are an important mechanism for respiratory pathogen transmission. Simple actions, like covering your mouth when coughing or sneezing, can reduce the spread of these microbes. (credit: modification of work by Centers for Disease Control and Prevention)

Chapter Outline

22.1 Anatomy and Normal Microbiota of the Respiratory Tract
22.2 Bacterial Infections of the Respiratory Tract
22.3 Viral Infections of the Respiratory Tract
22.4 Respiratory Mycoses

Introduction

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.\(^1\)

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 \textit{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.

22.1 Anatomy and Normal Microbiota of the Respiratory Tract

Learning Objectives

• Describe the major anatomical features of the upper and lower respiratory tract
• Describe the normal microbiota of the upper and lower respiratory tracts
• Explain how microorganisms overcome defenses of upper and lower respiratory-tract membranes to cause infection
• Explain how microbes and the respiratory system interact and modify each other in healthy individuals and during an infection

The primary function of the respiratory tract is to exchange gases (oxygen and carbon dioxide) for metabolism. However, inhalation and exhalation (particularly when forceful) can also serve as a vehicle of transmission for pathogens between individuals.

Anatomy of the Upper Respiratory System

The respiratory system can be conceptually divided into upper and lower regions at the point of the epiglottis, the structure that seals off the lower respiratory system from the pharynx during swallowing (Figure 22.2). The upper respiratory system is in direct contact with the external environment. The nares (or nostrils) are the external openings of the nose that lead back into the nasal cavity, a large air-filled space behind the nares. These anatomical sites constitute the primary opening and first section of the respiratory tract, respectively. The nasal cavity is lined with hairs that trap large particles, like dust and pollen, and prevent their access to deeper tissues. The nasal cavity is also lined with a mucous membrane and Bowman’s glands that produce mucus to help trap particles and microorganisms for removal. The nasal cavity is connected to several other air-filled spaces. The sinuses, a set of four, paired small cavities in the skull, communicate with the nasal cavity through a series of small openings. The nasopharynx is part of the upper throat extending from the posterior nasal cavity. The nasopharynx carries air inhaled through the nose. The middle ear is connected to the nasopharynx through the eustachian tube. The middle ear is separated from the outer ear by the tympanic membrane, or ear drum. And finally, the lacrimal glands drain to the nasal cavity through the nasolacrimal ducts (tear ducts). The open connections between these sites allow microorganisms to

Clinical Focus

Part 1

John, a 65-year-old man with asthma and type 2 diabetes, works as a sales associate at a local home improvement store. Recently, he began to feel quite ill and made an appointment with his family physician. At the clinic, John reported experiencing headache, chest pain, coughing, and shortness of breath. Over the past day, he had also experienced some nausea and diarrhea. A nurse took his temperature and found that he was running a fever of 40 °C (104 °F).

John suggested that he must have a case of influenza (flu), and regretted that he had put off getting his flu vaccine this year. After listening to John’s breathing through a stethoscope, the physician ordered a chest radiography and collected blood, urine, and sputum samples.

• Based on this information, what factors may have contributed to John’s illness?

Jump to the next Clinical Focus box.
move from the nasal cavity to the sinuses, middle ears (and back), and down into the lower respiratory tract from the nasopharynx.

The oral cavity is a secondary opening for the respiratory tract. The oral and nasal cavities connect through the fauces to the pharynx, or throat. The pharynx can be divided into three regions: the nasopharynx, the oropharynx, and the laryngopharynx. Air inhaled through the mouth does not pass through the nasopharynx; it proceeds first through the oropharynx and then through the laryngopharynx. The palatine tonsils, which consist of lymphoid tissue, are located within the oropharynx. The laryngopharynx, the last portion of the pharynx, connects to the larynx, which contains the vocal fold (Figure 22.2).

![Figure 22.2](image)

- Identify the sequence of anatomical structures through which microbes would pass on their way from the nares to the larynx.
- What two anatomical points do the eustachian tubes connect?

**Anatomy of the Lower Respiratory System**

The lower respiratory system begins below the epiglottis in the larynx or voice box (Figure 22.3). The trachea, or windpipe, is a cartilaginous tube extending from the larynx that provides an unobstructed path for air to reach the lungs. The trachea bifurcates into the left and right bronchi as it reaches the lungs. These paths branch repeatedly to form smaller and more extensive networks of tubes, the bronchioles. The terminal bronchioles formed in this tree-like network end in cul-de-sacs called the alveoli. These structures are surrounded by capillary networks and are the site of gas exchange in the respiratory system. Human lungs contain on the order of 400,000,000 alveoli. The outer surface of the lungs is protected with a double-layered pleural membrane. This structure protects the lungs and provides lubrication to permit the lungs to move easily during respiration.
Defenses of the Respiratory System

The inner lining of the respiratory system consists of mucous membranes (Figure 22.4) and is protected by multiple immune defenses. The goblet cells within the respiratory epithelium secrete a layer of sticky mucus. The viscosity and acidity of this secretion inhibits microbial attachment to the underlying cells. In addition, the respiratory tract contains ciliated epithelial cells. The beating cilia dislodge and propel the mucus, and any trapped microbes, upward to the epiglottis, where they will be swallowed. Elimination of microbes in this manner is referred to as the mucociliary escalator effect and is an important mechanism that prevents inhaled microorganisms from migrating further into the lower respiratory tract.
The upper respiratory system is under constant surveillance by mucosa-associated lymphoid tissue (MALT), including the adenoids and tonsils. Other mucosal defenses include secreted antibodies (IgA), lysozyme, surfactant, and antimicrobial peptides called defensins. Meanwhile, the lower respiratory tract is protected by alveolar macrophages. These phagocytes efficiently kill any microbes that manage to evade the other defenses. The combined action of these factors renders the lower respiratory tract nearly devoid of colonized microbes.

**Check Your Understanding**

- Identify the sequence of anatomical structures through which microbes would pass on their way from the larynx to the alveoli.
- Name some defenses of the respiratory system that protect against microbial infection.

**Normal Microbiota of the Respiratory System**

The upper respiratory tract contains an abundant and diverse microbiota. The nasal passages and sinuses are primarily colonized by members of the Firmicutes, Actinobacteria, and Proteobacteria. The most common bacteria identified include *Staphylococcus epidermidis*, viridans group streptococci (VGS), *Corynebacterium* spp. (diphtheroids), *Propionibacterium* spp., and *Haemophilus* spp. The oropharynx includes many of the same isolates as the nose and sinuses, with the addition of variable numbers of bacteria like species of *Prevotella, Fusobacterium, Moraxella*, and *Eikenella*, as well as some *Candida* fungal isolates. In addition, many healthy humans asymptptomatically carry potential pathogens in the upper respiratory tract. As much as 20% of the population carry *Staphylococcus aureus* in their nostrils.[2] The pharynx, too, can be colonized with pathogenic strains of *Streptococcus, Haemophilus*, and *Neisseria*.

---

The lower respiratory tract, by contrast, is scantily populated with microbes. Of the organisms identified in the lower respiratory tract, species of *Pseudomonas*, *Streptococcus*, *Prevotella*, *Fusobacterium*, and *Veillonella* are the most common. It is not clear at this time if these small populations of bacteria constitute a normal microbiota or if they are transients.

Many members of the respiratory system’s normal microbiota are opportunistic pathogens. To proliferate and cause host damage, they first must overcome the immune defenses of respiratory tissues. Many mucosal pathogens produce virulence factors such as adhesins that mediate attachment to host epithelial cells, or polysaccharide capsules that allow microbes to evade phagocytosis. The endotoxins of gram-negative bacteria can stimulate a strong inflammatory response that damages respiratory cells. Other pathogens produce exotoxins, and still others have the ability to survive within the host cells. Once an infection of the respiratory tract is established, it tends to impair the mucociliary escalator, limiting the body’s ability to expel the invading microbes, thus making it easier for pathogens to multiply and spread.

Vaccines have been developed for many of the most serious bacterial and viral pathogens. Several of the most important respiratory pathogens and their vaccines, if available, are summarized in Table 22.1. Components of these vaccines will be explained later in the chapter.

### Some Important Respiratory Diseases and Vaccines

<table>
<thead>
<tr>
<th>Disease</th>
<th>Pathogen</th>
<th>Available Vaccine(s)[3]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chickenpox/shingles</td>
<td>Varicella-zoster virus</td>
<td>Varicella (chickenpox) vaccine, herpes zoster (shingles) vaccine</td>
</tr>
<tr>
<td>Common cold</td>
<td>Rhinovirus</td>
<td>None</td>
</tr>
<tr>
<td>Diphtheria</td>
<td>Corynebacterium diphtheriae</td>
<td>DtaP, Tdap, DT, Td, DTP</td>
</tr>
<tr>
<td>Epiglottitis, otitis media</td>
<td><em>Haemophilus influenzae</em></td>
<td>Hib</td>
</tr>
<tr>
<td>Influenza</td>
<td>Influenza viruses</td>
<td>Inactivated, FluMist</td>
</tr>
<tr>
<td>Measles</td>
<td>Measles virus</td>
<td>MMR</td>
</tr>
<tr>
<td>Pertussis</td>
<td><em>Bordetella pertussis</em></td>
<td>DTaP, Tdap</td>
</tr>
<tr>
<td>Pneumonia</td>
<td><em>Streptococcus pneumoniae</em></td>
<td>Pneumococcal conjugate vaccine (PCV13), pneumococcal polysaccharide vaccine (PPSV23)</td>
</tr>
<tr>
<td>Rubella (German measles)</td>
<td>Rubella virus</td>
<td>MMR</td>
</tr>
<tr>
<td>Severe acute respiratory syndrome (SARS)</td>
<td>SARS-associated coronavirus (SARS-CoV)</td>
<td>None</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td><em>Mycobacterium tuberculosis</em></td>
<td>BCG</td>
</tr>
</tbody>
</table>

Table 22.1

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3. Full names of vaccines listed in table: *Haemophilus influenzae* type B (Hib); Diphtheria, tetanus, and acellular pertussis (DtaP); tetanus, diphtheria, and acellular pertussis (Tdap); diphtheria and tetanus (DT); tetanus and diphtheria (Td); diphtheria, pertussis, and tetanus (DTP); Bacillus Calmette-Guérin; Measles, mumps, rubella (MMR)
Check Your Understanding

- What are some pathogenic bacteria that are part of the normal microbiota of the respiratory tract?
- What virulence factors are used by pathogens to overcome the immune protection of the respiratory tract?

Signs and Symptoms of Respiratory Infection

Microbial diseases of the respiratory system typically result in an acute inflammatory response. These infections can be grouped by the location affected and have names ending in “itis”, which literally means inflammation of. For instance, rhinitis is an inflammation of the nasal cavities, often characteristic of the common cold. Rhinitis may also be associated with hay fever allergies or other irritants. Inflammation of the sinuses is called sinusitis inflammation of the ear is called otitis. Otitis media is an inflammation of the middle ear. A variety of microbes can cause pharyngitis, commonly known as a sore throat. An inflammation of the larynx is called laryngitis. The resulting inflammation may interfere with vocal cord function, causing voice loss. When tonsils are inflamed, it is called tonsillitis. Chronic cases of tonsillitis may be treated surgically with tonsillectomy. More rarely, the epiglottis can be infected, a condition called epiglottitis. In the lower respiratory system, the inflammation of the bronchial tubes results in bronchitis. Most serious of all is pneumonia, in which the alveoli in the lungs are infected and become inflamed. Pus and edema accumulate and fill the alveoli with fluids (called consolidations). This reduces the lungs’ ability to exchange gases and often results in a productive cough expelling phlegm and mucus. Cases of pneumonia can range from mild to life-threatening, and remain an important cause of mortality in the very young and very old.

Check Your Understanding

- Describe the typical symptoms of rhinitis, sinusitis, pharyngitis, and laryngitis.

Case in Point

Smoking-Associated Pneumonia

Camila is a 22-year-old student who has been a chronic smoker for 5 years. Recently, she developed a persistent cough that has not responded to over-the-counter treatments. Her doctor ordered a chest radiograph to investigate. The radiological results were consistent with pneumonia. In addition, Streptococcus pneumoniae was isolated from Camila’s sputum.

Smokers are at a greater risk of developing pneumonia than the general population. Several components of tobacco smoke have been demonstrated to impair the lungs’ immune defenses. These effects include disrupting the function of the ciliated epithelial cells, inhibiting phagocytosis, and blocking the action of antimicrobial peptides. Together, these lead to a dysfunction of the mucociliary escalator effect. The organisms trapped in the mucus are therefore able to colonize the lungs and cause infections rather than being expelled or swallowed.
22.2 Bacterial Infections of the Respiratory Tract

Learning Objectives

• Identify the most common bacteria that can cause infections of the upper and lower respiratory tract
• Compare the major characteristics of specific bacterial diseases of the respiratory tract

The respiratory tract can be infected by a variety of bacteria, both gram positive and gram negative. Although the diseases that they cause may range from mild to severe, in most cases, the microbes remain localized within the respiratory system. Fortunately, most of these infections also respond well to antibiotic therapy.

Streptococcal Infections

A common upper respiratory infection, streptococcal pharyngitis (strep throat) is caused by *Streptococcus pyogenes*. This gram-positive bacterium appears as chains of cocci, as seen in Figure 22.5. Rebecca Lancefield serologically classified streptococci in the 1930s using carbohydrate antigens from the bacterial cell walls. *S. pyogenes* is the sole member of the Lancefield group A streptococci and is often referred to as GAS, or group A strep.

![Figure 22.5](credit: modification of work by U.S. Centers for Disease Control and Prevention - Medical Illustrator)

Similar to streptococcal infections of the skin, the mucosal membranes of the pharynx are damaged by the release of a variety of exoenzymes and exotoxins by this extracellular pathogen. Many strains of *S. pyogenes* can degrade connective tissues by using hyaluronidase, collagenase and streptokinase. Streptokinase activates plasmin, which leads to degradation of fibrin and, in turn, dissolution of blood clots, which assists in the spread of the pathogen. Released toxins include streptolysins that can destroy red and white blood cells. The classic signs of streptococcal pharyngitis are a fever higher than 38 °C (100.4 °F); intense pharyngeal pain; erythema associated with pharyngeal inflammation; and swollen, dark-red palatine tonsils, often dotted with patches of pus; and petechiae (microcapillary hemorrhages) on the soft or hard palate (roof of the mouth) (Figure 22.6). The submandibular lymph nodes beneath the angle of the jaw are also often swollen during strep throat.

Some strains of group A streptococci produce erythrogenic toxin. This exotoxin is encoded by a temperate bacteriophage (bacterial virus) and is an example of phage conversion (see The Viral Life Cycle). The toxin attacks the plasma membranes of capillary endothelial cells and leads to scarlet fever (or scarlatina), a disseminated fine red rash on the skin, and strawberry tongue, a red rash on the tongue (Figure 22.6). Severe cases may even lead to
streptococcal toxic shock syndrome (STSS), which results from massive superantigen production that leads to septic shock and death.

*S. pyogenes* can be easily spread by direct contact or droplet transmission through coughing and sneezing. The disease can be diagnosed quickly using a rapid enzyme immunoassay for the group A antigen. However, due to a significant rate of false-negative results (up to 30%[^4]), culture identification is still the gold standard to confirm pharyngitis due to *S. pyogenes*. *S. pyogenes* can be identified as a catalase-negative, beta hemolytic bacterium that is susceptible to 0.04 units of bacitracin. Antibiotic resistance is limited for this bacterium, so most β-lactams remain effective; oral amoxicillin and intramuscular penicillin G are those most commonly prescribed.

![Streptococcal Infections of the Respiratory Tract](image)

**Figure 22.6** Streptococcal infections of the respiratory tract may cause localized pharyngitis or systemic signs and symptoms. (a) The characteristic appearance of strep throat: bright red arches of inflammation with the presence of dark-red spots (petechiae). (b) Scarlet fever presents as a rash on the skin. (credit a: modification of work by Centers for Disease Control and Prevention; credit b: modification of work by Alicia Williams)

### Sequelae of *S. pyogenes* Infections

One reason strep throat infections are aggressively treated with antibiotics is because they can lead to serious sequelae, later clinical consequences of a primary infection. It is estimated that 1%–3% of untreated *S. pyogenes* infections can be followed by nonsuppurative (without the production of pus) sequelae that develop 1–3 weeks after the acute infection has resolved. Two such sequelae are **acute rheumatic fever** and **acute glomerulonephritis**.

Acute rheumatic fever can follow pharyngitis caused by specific rheumatogenic strains of *S. pyogenes* (strains 1, 3, 5, 6, and 18). Although the exact mechanism responsible for this sequela remains unclear, molecular mimicry between the M protein of rheumatogenic strains of *S. pyogenes* and heart tissue is thought to initiate the autoimmune attack. The most serious and lethal clinical manifestation of rheumatic fever is damage to and inflammation of the heart (carditis). Acute glomerulonephritis also results from an immune response to streptococcal antigens following pharyngitis and cutaneous infections. Acute glomerulonephritis develops within 6–10 days after pharyngitis, but can take up to 21 days after a cutaneous infection. Similar to acute rheumatic fever, there are strong associations between specific nephritogenic strains of *S. pyogenes* and acute glomerulonephritis, and evidence suggests a role for antigen mimicry and autoimmunity. However, the primary mechanism of acute glomerulonephritis appears to be the formation of immune complexes between *S. pyogenes* antigens and antibodies, and their deposition between endothelial cells of the glomeruli of kidney. Inflammatory response against the immune complexes leads to damage and inflammation of the glomeruli (glomerulonephritis).

Acute Otitis Media

An infection of the middle ear is called acute otitis media (AOM), but often it is simply referred to as an earache. The condition is most common between ages 3 months and 3 years. In the United States, AOM is the second-leading cause of visits to pediatricians by children younger than age 5 years, and it is the leading indication for antibiotic prescription.[5]

AOM is characterized by the formation and accumulation of pus in the middle ear. Unable to drain, the pus builds up, resulting in moderate to severe bulging of the tympanic membrane and otalgia (ear pain). Inflammation resulting from the infection leads to swelling of the eustachian tubes, and may also lead to fever, nausea, vomiting, and diarrhea, particularly in infants. Infants and toddlers who cannot yet speak may exhibit nonverbal signs suggesting AOM, such as holding, tugging, or rubbing of the ear, as well as uncharacteristic crying or distress in response to the pain.

AOM can be caused by a variety of bacteria. Among neonates, *S. pneumoniae* is the most common cause of AOM, but *Escherichia coli*, *Enterococcus* spp., and group B *Streptococcus* species can also be involved. In older infants and children younger than 14 years old, the most common bacterial causes are *S. pneumoniae*, *Haemophilus influenzae*, or *Moraxella catarrhalis*. Among *S. pneumoniae* infections, encapsulated strains are frequent causes of AOM. By contrast, the strains of *H. influenzae* and *M. catarrhalis* that are responsible for AOM do not possess a capsule. Rather than direct tissue damage by these pathogens, bacterial components such as lipopolysaccharide (LPS) in gram-negative pathogens induce an inflammatory response that causes swelling, pus, and tissue damage within the middle ear (Figure 22.7).

Any blockage of the eustachian tubes, with or without infection, can cause fluid to become trapped and accumulate in the middle ear. This is referred to as otitis media with effusion (OME). The accumulated fluid offers an excellent reservoir for microbial growth and, consequently, secondary bacterial infections often ensue. This can lead to recurring and chronic earaches, which are especially common in young children. The higher incidence in children can be attributed to many factors. Children have more upper respiratory infections, in general, and their eustachian tubes are also shorter and drain at a shallower angle. Young children also tend to spend more time lying down than adults, which facilitates drainage from the nasopharynx through the eustachian tube and into the middle ear. Bottle feeding while lying down enhances this risk because the sucking action on the bottle causes negative pressure to build up within the eustachian tube, promoting the movement of fluid and bacteria from the nasopharynx.

Diagnosis is typically made based on clinical signs and symptoms, without laboratory testing to determine the specific causative agent. Antibiotics are frequently prescribed for the treatment of AOM. High-dose amoxicillin is the first-line drug, but with increasing resistance concerns, macrolides and cephalosporins may also be used. The pneumococcal conjugate vaccine (PCV13) contains serotypes that are important causes of AOM, and vaccination has been shown to decrease the incidence of AOM. Vaccination against influenza has also been shown to decrease the risk for AOM, likely because viral infections like influenza predispose patients to secondary infections with *S. pneumoniae*. Although there is a conjugate vaccine available for the invasive serotype B of *H. influenzae*, this vaccine does not impact the incidence of *H. influenzae* AOM. Because unencapsulated strains of *H. influenzae* and *M. catarrhalis* are involved in AOM, vaccines against bacterial cellular factors other than capsules will need to be developed.

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Bacterial Rhinosinusitis

The microbial community of the nasopharynx is extremely diverse and harbors many opportunistic pathogens, so it is perhaps not surprising that infections leading to rhinitis and sinusitis have many possible causes. These conditions often occur as secondary infections after a viral infection, which effectively compromises the immune defenses and allows the opportunistic bacteria to establish themselves. Bacterial sinusitis involves infection and inflammation within the paranasal sinuses. Because bacterial sinusitis rarely occurs without rhinitis, the preferred term is rhinosinusitis. The most common causes of bacterial rhinosinusitis are similar to those for AOM, including *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*.

**Check Your Understanding**

- What are the usual causative agents of acute otitis media?
- What factors facilitate acute otitis media with effusion in young children?
- What factor often triggers bacterial rhinosinusitis?

**Diphtheria**

The causative agent of diphtheria, *Corynebacterium diphtheriae*, is a club-shaped, gram-positive rod that belongs to the phylum Actinobacteria. Diphtheroids are common members of the normal nasopharyngeal microbiota. However, some strains of *C. diphtheriae* become pathogenic because of the presence of a temperate bacteriophage-encoded protein—the diphtheria toxin. Diphtheria is typically a respiratory infection of the oropharynx but can also cause impetigo-like lesions on the skin. Although the disease can affect people of all ages, it tends to be most severe in those younger than 5 years or older than 40 years. Like strep throat, diphtheria is commonly transmitted in the droplets and aerosols produced by coughing. After colonizing the throat, the bacterium remains in the oral cavity and begins
producing the diphtheria toxin. This protein is an A-B toxin that blocks host-cell protein synthesis by inactivating elongation factor (EF)-2 (see Virulence Factors of Bacterial and Viral Pathogens). The toxin’s action leads to the death of the host cells and an inflammatory response. An accumulation of grayish exudate consisting of dead host cells, pus, red blood cells, fibrin, and infectious bacteria results in the formation of a pseudomembrane. The pseudomembrane can cover mucous membranes of the nasal cavity, tonsils, pharynx, and larynx (Figure 22.8). This is a classic sign of diphtheria. As the disease progresses, the pseudomembrane can enlarge to obstruct the fauces of the pharynx or trachea and can lead to suffocation and death. Sometimes, intubation, the placement of a breathing tube in the trachea, is required in advanced infections. If the diphtheria toxin spreads throughout the body, it can damage other tissues as well. This can include myocarditis (heart damage) and nerve damage that may impair breathing.

![pseudomembrane](credit: modification of work by Putnong N, Agustin G, Pasubillo M, Miyagi K, Dimaano EM)

**Figure 22.8** The pseudomembrane in a patient with diphtheria presents as a leathery gray patch consisting of dead cells, pus, fibrin, red blood cells, and infectious microbes. (credit: modification of work by Putnong N, Agustin G, Pasubillo M, Miyagi K, Dimaano EM)

The presumptive diagnosis of diphtheria is primarily based on the clinical symptoms (i.e., the pseudomembrane) and vaccination history, and is typically confirmed by identifying bacterial cultures obtained from throat swabs. The diphtheria toxin itself can be directly detected in vitro using polymerase chain reaction (PCR)-based, direct detection systems for the diphtheria tox gene, and immunological techniques like radial immunodiffusion or Elek’s immunodiffusion test.

Broad-spectrum antibiotics like penicillin and erythromycin tend to effectively control *C. diphtheriae* infections. Regrettably, they have no effect against preformed toxins. If toxin production has already occurred in the patient, antitoxins (preformed antibodies against the toxin) are administered. Although this is effective in neutralizing the toxin, the antitoxins may lead to serum sickness because they are produced in horses (see Hypersensitivities).

Widespread vaccination efforts have reduced the occurrence of diphtheria worldwide. There are currently four combination toxoid vaccines available that provide protection against diphtheria and other diseases: DTaP, Tdap, DT, and Td. In all cases, the letters “d,” “t,” and “p” stand for diphtheria, tetanus, and pertussis, respectively; the “a” stands for acellular. If capitalized, the letters indicate a full-strength dose; lowercase letters indicate reduced dosages. According to current recommendations, children should receive five doses of the DTaP vaccine in their youth and a Td booster every 10 years. Children with adverse reactions to the pertussis vaccine may be given the DT vaccine in place of the DTaP.
Check Your Understanding

- What effect does diphtheria toxin have?
- What is the pseudomembrane composed of?

Bacterial Pneumonia

Pneumonia is a general term for infections of the lungs that lead to inflammation and accumulation of fluids and white blood cells in the alveoli. Pneumonia can be caused by bacteria, viruses, fungi, and other organisms, although the vast majority of pneumonias are bacterial in origin. Bacterial pneumonia is a prevalent, potentially serious infection; it caused more than 50,000 deaths in the United States in 2014. As the alveoli fill with fluids and white blood cells (consolidation), air exchange becomes impaired and patients experience respiratory distress (Figure 22.9). In addition, pneumonia can lead to pleurisy, an infection of the pleural membrane surrounding the lungs, which can make breathing very painful. Although many different bacteria can cause pneumonia under the right circumstances, three bacterial species cause most clinical cases: *Streptococcus pneumoniae*, *H. influenzae*, and *Mycoplasma pneumoniae*. In addition to these, we will also examine some of the less common causes of pneumonia.

Figure 22.9  A chest radiograph of a patient with pneumonia shows the consolidations (lesions) present as opaque patches. (credit: modification of work by Centers for Disease Control and Prevention)

Pneumococcal Pneumonia

The most common cause of community-acquired bacterial pneumonia is *Streptococcus pneumoniae*. This gram-positive, alpha hemolytic streptococcus is commonly found as part of the normal microbiota of the human respiratory tract. The cells tend to be somewhat lancet-shaped and typically appear as pairs (Figure 22.10). The pneumococci initially colonize the bronchioles of the lungs. Eventually, the infection spreads to the alveoli, where the microbe’s polysaccharide capsule interferes with phagocytic clearance. Other virulence factors include autolysins like Lyt A, which degrade the microbial cell wall, resulting in cell lysis and the release of cytoplasmic virulence factors. One of these factors, pneumolysin O, is important in disease progression; this pore-forming protein damages host cells, promotes bacterial adherence, and enhances pro-inflammatory cytokine production. The resulting inflammatory response causes the alveoli to fill with exudate rich in neutrophils and red blood cells. As a consequence, infected individuals develop a productive cough with bloody sputum.

Pneumococci can be presumptively identified by their distinctive gram-positive, lancet-shaped cell morphology and diplococcal arrangement. In blood agar cultures, the organism demonstrates alpha hemolytic colonies that are autolytic after 24 to 48 hours. In addition, *S. pneumoniae* is extremely sensitive to optochin and colonies are rapidly destroyed by the addition of 10% solution of sodium deoxycholate. All clinical pneumococcal isolates are serotyped using the quellung reaction with typing antisera produced by the CDC. Positive quellung reactions are considered definitive identification of pneumococci.

Antibiotics remain the mainstay treatment for pneumococci. β-Lactams like penicillin are the first-line drugs, but resistance to β-lactams is a growing problem. When β-lactam resistance is a concern, macrolides and fluoroquinolones may be prescribed. However, *S. pneumoniae* resistance to macrolides and fluoroquinolones is increasing as well, limiting the therapeutic options for some infections. There are currently two pneumococcal vaccines available: pneumococcal conjugate vaccine (PCV13) and pneumococcal polysaccharide vaccine (PPSV23). These are generally given to the most vulnerable populations of individuals: children younger than 2 years and adults older than 65 years.

**Haemophilus Pneumonia**

Encapsulated strains of *Haemophilus influenzae* are known for causing meningitis, but nonencapsulated strains are important causes of pneumonia. This small, gram-negative coccobacillus is found in the pharynx of the majority of healthy children; however, *Haemophilus* pneumonia is primarily seen in the elderly. Like other pathogens that cause pneumonia, *H. influenzae* is spread by droplets and aerosols produced by coughing. A fastidious organism, *H. influenzae* will only grow on media with available factor X (hemin) and factor V (NAD), like chocolate agar (Figure 22.11). Serotyping must be performed to confirm identity of *H. influenzae* isolates.

Infections of the alveoli by *H. influenzae* result in inflammation and accumulation of fluids. Increasing resistance to β-lactams, macrolides, and tetracyclines presents challenges for the treatment of *Haemophilus* pneumonia. Resistance to the fluoroquinolones is rare among isolates of *H. influenzae* but has been observed. As discussed for AOM, a vaccine directed against nonencapsulated *H. influenzae*, if developed, would provide protection against pneumonia caused by this pathogen.
Tracy is a 6-year old who developed a serious cough that would not seem to go away. After 2 weeks, her parents became concerned and took her to the pediatrician, who suspected a case of bacterial pneumonia. Tests confirmed that the cause was *Haemophilus influenzae*. Fortunately, Tracy responded well to antibiotic treatment and eventually made a full recovery.

Because there had been several other cases of bacterial pneumonia at Tracy's elementary school, local health officials urged parents to have their children screened. Of the children who were screened, it was discovered that greater than 50% carried *H. influenzae* in their nasal cavities, yet all but two of them were asymptomatic.

Why is it that some individuals become seriously ill from bacterial infections that seem to have little or no effect on others? The pathogenicity of an organism—its ability to cause host damage—is not solely a property of the microorganism. Rather, it is the product of a complex relationship between the microbe's virulence factors and the immune defenses of the individual. Preexisting conditions and environmental factors such as exposure to secondhand smoke can make some individuals more susceptible to infection by producing conditions favorable to microbial growth or compromising the immune system. In addition, individuals may have genetically determined immune factors that protect them—or not—from particular strains of pathogens. The interactions between these host factors and the pathogenicity factors produced by the microorganism ultimately determine the outcome of the infection. A clearer understanding of these interactions may allow for better identification of at-risk individuals and prophylactic interventions in the future.

*Mycoplama Pneumonia (Walking Pneumonia)*

Primary atypical pneumonia is caused by *Mycoplasma pneumoniae*. This bacterium is not part of the respiratory tract’s normal microbiota and can cause epidemic disease outbreaks. Also known as walking pneumonia, *mycoplasma pneumoniae* infections are common in crowded environments like college campuses and military bases. It is spread by aerosols formed when coughing or sneezing. The disease is often mild, with a low fever and persistent cough. These bacteria, which do not have cell walls, use a specialized attachment organelle to bind to ciliated cells. In the process, epithelial cells are damaged and the proper function of the cilia is hindered (Figure 22.12).
Mycoplasma grow very slowly when cultured. Therefore, penicillin and thallium acetate are added to agar to prevent the overgrowth by faster-growing potential contaminants. Since *M. pneumoniae* does not have a cell wall, it is resistant to these substances. Without a cell wall, the microbial cells appear pleomorphic. *M. pneumoniae* infections tend to be self-limiting but may also respond well to macrolide antibiotic therapy. β-lactams, which target cell wall synthesis, are not indicated for treatment of infections with this pathogen.

![Figure 22.12](image)

**Figure 22.12** The micrograph shows *Mycoplasma pneumoniae* using their specialized receptors to attach to epithelial cells in the trachea of an infected hamster. (credit: modification of work by American Society for Microbiology)

**Chlamydial Pneumonias and Psittacosis**

Chlamydial pneumonia can be caused by three different species of bacteria: *Chlamydophila pneumoniae* (formerly known as *Chlamydia pneumoniae*), *Chlamydophila psittaci* (formerly known as *Chlamydia psittaci*), and *Chlamydia trachomatis*. All three are obligate intracellular pathogens and cause mild to severe pneumonia and bronchitis. Of the three, *Chlamydophila pneumoniae* is the most common and is transmitted via respiratory droplets or aerosols. *C. psittaci* causes psittacosis, a zoonotic disease that primarily affects domesticated birds such as parakeets, turkeys, and ducks, but can be transmitted from birds to humans. Psittacosis is a relatively rare infection and is typically found in people who work with birds. *Chlamydia trachomatis*, the causative agent of the sexually transmitted disease chlamydia, can cause pneumonia in infants when the infection is passed from mother to baby during birth.

Diagnosis of chlamydia by culturing tends to be difficult and slow. Because they are intracellular pathogens, they require multiple passages through tissue culture. Recently, a variety of PCR- and serologically based tests have been developed to enable easier identification of these pathogens. Tetracycline and macrolide antibiotics are typically prescribed for treatment.

**Health Care-Associated Pneumonia**

A variety of opportunistic bacteria that do not typically cause respiratory disease in healthy individuals are common causes of health care-associated pneumonia. These include *Klebsiella pneumoniae*, *Staphylococcus aureus*, and proteobacteria such as species of *Escherichia*, *Proteus*, and *Serratia*. Patients at risk include the elderly, those who have other preexisting lung conditions, and those who are immunocompromised. In addition, patients receiving supportive therapies such as intubation, antibiotics, and immunomodulatory drugs may also be at risk because these interventions disrupt the mucociliary escalator and other pulmonary defenses. Invasive medical devices such as
catheters, medical implants, and ventilators can also introduce opportunistic pneumonia-causing pathogens into the body.\textsuperscript{[7]}

Pneumonia caused by \textit{K. pneumoniae} is characterized by lung necrosis and “currant jelly sputum,” so named because it consists of clumps of blood, mucus, and debris from the thick polysaccharide capsule produced by the bacterium. \textit{K. pneumoniae} is often multidrug resistant. Aminoglycoside and cephalosporin are often prescribed but are not always effective. \textit{Klebsiella} pneumonia is frequently fatal even when treated.

\textbf{Pseudomonas Pneumonia}

\textit{Pseudomonas aeruginosa} is another opportunistic pathogen that can cause serious cases of bacterial pneumonia in patients with cystic fibrosis (CF) and hospitalized patients assisted with artificial ventilators. This bacterium is extremely antibiotic resistant and can produce a variety of exotoxins. Ventilator-associated pneumonia with \textit{P. aeruginosa} is caused by contaminated equipment that causes the pathogen to be aspirated into the lungs. In patients with CF, a genetic defect in the cystic fibrosis transmembrane receptor (CFTR) leads to the accumulation of excess dried mucus in the lungs. This decreases the effectiveness of the defensins and inhibits the mucociliary escalator. \textit{P. aeruginosa} is known to infect more than half of all patients with CF. It adapts to the conditions in the patient’s lungs and begins to produce alginate, a viscous exopolysaccharide that inhibits the mucociliary escalator. Lung damage from the chronic inflammatory response that ensues is the leading cause of mortality in patients with CF.\textsuperscript{[8]}

\section*{Check Your Understanding}

- What three pathogens are responsible for the most prevalent types of bacterial pneumonia?
- Which cause of pneumonia is most likely to affect young people?
- In what contexts does \textit{Pseudomonas aeruginosa} cause pneumonia?

\section*{Clinical Focus}

\textbf{Part 2}

John’s chest radiograph revealed an extensive consolidation in the right lung, and his sputum cultures revealed the presence of a gram-negative rod. His physician prescribed a course of the antibiotic clarithromycin. He also ordered the rapid influenza diagnostic tests (RIDTs) for type A and B influenza to rule out a possible underlying viral infection. Despite antibiotic therapy, John’s condition continued to deteriorate, so he was admitted to the hospital.

- What are some possible causes of pneumonia that would not have responded to the prescribed antibiotic?

\textit{Jump to the next Clinical Focus box. Go back to the previous Clinical Focus box.}

\section*{Tuberculosis}

Tuberculosis (TB) is one of the deadliest infectious diseases in human history. Although \textbf{tuberculosis} infection rates in the United States are extremely low, the CDC estimates that about one-third of the world’s population is infected.

\begin{thebibliography}{9}
\end{thebibliography}
with *Mycobacterium tuberculosis*, the causal organism of TB, with 9.6 million new TB cases and 1.5 million deaths worldwide in 2014.[9]

*M. tuberculosis* is an acid-fast, high G + C, gram-positive, nonspore-forming rod. Its cell wall is rich in waxy mycolic acids, which make the cells impervious to polar molecules. It also causes these organisms to grow slowly. *M. tuberculosis* causes a chronic granulomatous disease that can infect any area of the body, although it is typically associated with the lungs. *M. tuberculosis* is spread by inhalation of respiratory droplets or aerosols from an infected person. The infectious dose of *M. tuberculosis* is only 10 cells.[10]

After inhalation, the bacteria enter the alveoli (Figure 22.13). The cells are phagocytized by macrophages but can survive and multiply within these phagocytes because of the protection by the waxy mycolic acid in their cell walls. If not eliminated by macrophages, the infection can progress, causing an inflammatory response and an accumulation of neutrophils and macrophages in the area. Several weeks or months may pass before an immunological response is mounted by T cells and B cells. Eventually, the lesions in the alveoli become walled off, forming small round lesions called tubercles. Bacteria continue to be released into the center of the tubercles and the chronic immune response results in tissue damage and induction of apoptosis (programmed host-cell death) in a process called liquefaction. This creates a caseous center, or air pocket, where the aerobic *M. tuberculosis* can grow and multiply. Tubercles may eventually rupture and bacterial cells can invade pulmonary capillaries; from there, bacteria can spread through the bloodstream to other organs, a condition known as miliary tuberculosis. The rupture of tubercles also facilitates transmission of the bacteria to other individuals via droplet aerosols that exit the body in coughs. Because these droplets can be very small and stay aloft for a long time, special precautions are necessary when caring for patients with TB, such as the use of face masks and negative-pressure ventilation and filtering systems.

Eventually, most lesions heal to form calcified Ghon complexes. These structures are visible on chest radiographs and are a useful diagnostic feature. But even after the disease has apparently ended, viable bacteria remain sequestered in these locations. Release of these organisms at a later time can produce reactivation tuberculosis (or secondary TB). This is mainly observed in people with alcoholism, the elderly, or in otherwise immunocompromised individuals (Figure 22.13).

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In the infectious cycle of tuberculosis, the immune response of most infected individuals (approximately 90%) results in the formation of tubercles in which the infection is walled off. The remainder will suffer progressive primary tuberculosis. The sequestered bacteria may be reactivated to form secondary tuberculosis in immunocompromised patients at a later time. (credit: modification of work by Centers for Disease Control and Prevention)

Because TB is a chronic disease, chemotherapeutic treatments often continue for months or years. Multidrug resistant (MDR-TB) and extensively drug-resistant (XDR-TB) strains of \textit{M. tuberculosis} are a growing clinical concern. These strains can arise due to misuse or mismanagement of antibiotic therapies. Therefore, it is imperative that proper

multidrug protocols are used to treat these infections. Common antibiotics included in these mixtures are isoniazid, rifampin, ethambutol, and pyrazinamide.

A TB vaccine is available that is based on the so-called bacillus Calmette-Guérin (BCG) strain of M. bovis commonly found in cattle. In the United States, the BCG vaccine is only given to health-care workers and members of the military who are at risk of exposure to active cases of TB. It is used more broadly worldwide. Many individuals born in other countries have been vaccinated with BCG strain. BCG is used in many countries with a high prevalence of TB, to prevent childhood tuberculous meningitis and miliary disease.

The Mantoux tuberculin skin test (Figure 22.14) is regularly used in the United States to screen for potential TB exposure (see Hypersensitivities). However, prior vaccinations with the BCG vaccine can cause false-positive results. Chest radiographs to detect Ghon complex formation are required, therefore, to confirm exposure.

Figure 22.14  (a) The Mantoux skin test for tuberculosis involves injecting the subject with tuberculin protein derivative. The injection should initially produce a raised wheal. (b) The test should be read in 48–72 hours. A positive result is indicated by redness, swelling, or hardness; the size of the responding region is measured to determine the final result. (credit a, b: modification of work by Centers for Disease Control and Prevention)

These short animations (https://openstax.org/l/22mycotublegpnean) discuss the infection strategies of Mycobacterium tuberculosis and Legionella pneumophila.

Check Your Understanding

- What characteristic of Mycobacterium tuberculosis allows it to evade the immune response?
- What happens to cause miliary tuberculosis?
- Explain the limitations of the Mantoux tuberculin skin test.

Pertussis (Whooping Cough)

The causative agent of pertussis, commonly called whooping cough, is Bordetella pertussis, a gram-negative coccobacillus. The disease is characterized by mucus accumulation in the lungs that leads to a long period of severe coughing. Sometimes, following a bout of coughing, a sound resembling a “whoop” is produced as air is inhaled.
through the inflamed and restricted airway—hence the name whooping cough. Although adults can be infected, the symptoms of this disease are most pronounced in infants and children. Pertussis is highly communicable through droplet transmission, so the uncontrollable coughing produced is an efficient means of transmitting the disease in a susceptible population.

Following inhalation, *B. pertussis* specifically attaches to epithelial cells using an adhesin, filamentous hemagglutinin. The bacteria then grow at the site of infection and cause disease symptoms through the production of exotoxins. One of the main virulence factors of this organism is an A-B exotoxin called the pertussis toxin (PT). When PT enters the host cells, it increases the cyclic adenosine monophosphate (cAMP) levels and disrupts cellular signaling. PT is known to enhance inflammatory responses involving histamine and serotonin. In addition to PT, *B. pertussis* produces a tracheal cytotoxin that damages ciliated epithelial cells and results in accumulation of mucus in the lungs. The mucus can support the colonization and growth of other microbes and, as a consequence, secondary infections are common. Together, the effects of these factors produce the cough that characterizes this infection.

A pertussis infection can be divided into three distinct stages. The initial infection, termed the **catarrhal stage**, is relatively mild and unremarkable. The signs and symptoms may include nasal congestion, a runny nose, sneezing, and a low-grade fever. This, however, is the stage in which *B. pertussis* is most infectious. In the **paroxysmal stage**, mucus accumulation leads to uncontrollable coughing spasms that can last for several minutes and frequently induce vomiting. The paroxysmal stage can last for several weeks. A long **convalescence stage** follows the paroxysmal stage, during which time patients experience a chronic cough that can last for up to several months. In fact, the disease is sometimes called the 100-day cough.

In infants, coughing can be forceful enough to cause fractures to the ribs, and prolonged infections can lead to death. The CDC reported 20 pertussis-related deaths in 2012, but that number had declined to five by 2015.

During the first 2 weeks of infection, laboratory diagnosis is best performed by culturing the organism directly from a nasopharyngeal (NP) specimen collected from the posterior nasopharynx. The NP specimen is streaked onto Bordet-Gengou medium. The specimens must be transported to the laboratory as quickly as possible, even if transport media are used. Transport times of longer than 24 hours reduce the viability of *B. pertussis* significantly.

Within the first month of infection, *B. pertussis* can be diagnosed using PCR techniques. During the later stages of infection, pertussis-specific antibodies can be immunologically detected using an enzyme-linked immunosorbent assay (ELISA).

Pertussis is generally a self-limiting disease. Antibiotic therapy with erythromycin or tetracycline is only effective at the very earliest stages of disease. Antibiotics given later in the infection, and prophylactically to uninfected individuals, reduce the rate of transmission. Active vaccination is a better approach to control this disease. The DPT vaccine was once in common use in the United States. In that vaccine, the P component consisted of killed whole-cell *B. pertussis* preparations. Because of some adverse effects, that preparation has now been superseded by the DTaP and Tdap vaccines. In both of these new vaccines, the “aP” component is a pertussis toxoid.

Widespread vaccination has greatly reduced the number of reported cases and prevented large epidemics of pertussis. Recently, however, pertussis has begun to reemerge as a childhood disease in some states because of declining vaccination rates and an increasing population of susceptible children.

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Legionnaires Disease

An atypical pneumonia called Legionnaires disease (also known as legionellosis) is caused by an aerobic gram-negative bacillus, Legionella pneumophila. This bacterium infects free-living amoebae that inhabit moist environments, and infections typically occur from human-made reservoirs such as air-conditioning cooling towers, humidifiers, misting systems, and fountains. Aerosols from these reservoirs can lead to infections of susceptible individuals, especially those suffering from chronic heart or lung disease or other conditions that weaken the immune system.

When *L. pneumophila* bacteria enter the alveoli, they are phagocytized by resident macrophages. However, *L. pneumophila* uses a secretion system to insert proteins in the endosomal membrane of the macrophage; these proteins prevent lysosomal fusion, allowing *L. pneumophila* to continue to proliferate within the phagosome. The resulting respiratory disease can range from mild to severe pneumonia, depending on the status of the host’s immune defenses. Although this disease primarily affects the lungs, it can also cause fever, nausea, vomiting, confusion, and other neurological effects.

Diagnosis of Legionnaires disease is somewhat complicated. *L. pneumophila* is a fastidious bacterium and is difficult to culture. In addition, since the bacterial cells are not efficiently stained with the Gram stain, other staining techniques, such as the Warthin-Starry silver-precipitate procedure, must be used to visualize this pathogen. A rapid diagnostic test has been developed that detects the presence of *Legionella* antigen in a patient’s urine; results take less than 1 hour, and the test has high selectivity and specificity (greater than 90%). Unfortunately, the test only works for one serotype of *L. pneumophila* (type 1, the serotype responsible for most infections). Consequently, isolation and identification of *L. pneumophila* from sputum remains the defining test for diagnosis.

Once diagnosed, Legionnaire disease can be effectively treated with fluoroquinolone and macrolide antibiotics. However, the disease is sometimes fatal; about 10% of patients die of complications.\(^{14}\) There is currently no vaccine available.

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Q Fever

The zoonotic disease Q fever is caused by a rickettsia, Coxiella burnetii. The primary reservoirs for this bacterium are domesticated livestock such as cattle, sheep, and goats. The bacterium may be transmitted by ticks or through exposure to the urine, feces, milk, or amniotic fluid of an infected animal. In humans, the primary route of infection is through inhalation of contaminated farmyard aerosols. It is, therefore, largely an occupational disease of farmers. Humans are acutely sensitive to C. burnetii—the infective dose is estimated to be just a few cells.\(^\text{15}\) In addition, the organism is hardy and can survive in a dry environment for an extended time. Symptoms associated with acute Q fever include high fever, headache, coughing, pneumonia, and general malaise. In a small number of patients (less than 5\(^\text{\%}\)), the condition may become chronic, often leading to endocarditis, which may be fatal.

Diagnosing rickettsial infection by cultivation in the laboratory is both difficult and hazardous because of the easy aerosolization of the bacteria, so PCR and ELISA are commonly used. Doxycycline is the first-line drug to treat acute Q fever. In chronic Q fever, doxycycline is often paired with hydroxychloroquine.

Disease Profile

Bacterial Diseases of the Respiratory Tract

Numerous pathogens can cause infections of the respiratory tract. Many of these infections produce similar signs and symptoms, but appropriate treatment depends on accurate diagnosis through laboratory testing. The tables in Figure 22.15 and Figure 22.16 summarize the most important bacterial respiratory infections, with the latter focusing specifically on forms of bacterial pneumonia.
## Bacterial Infections of the Respiratory Tract

<table>
<thead>
<tr>
<th>Disease</th>
<th>Pathogen</th>
<th>Signs and Symptoms</th>
<th>Transmission</th>
<th>Diagnostic Tests</th>
<th>Antimicrobial Drugs</th>
<th>Vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute otitis media (AOM)</td>
<td><em>Haemophilus influenzae,</em> <em>S. pneumoniae,</em> <em>M. catarrhalis,</em> others</td>
<td>Earache, possible effusion; may cause fever, nausea, vomiting, diarrhea</td>
<td>Often a secondary infection; bacteria from respiratory tract become trapped in eustachian tube, cause infection</td>
<td>None</td>
<td>Cephalexin, chloramphenicol</td>
<td>None</td>
</tr>
<tr>
<td>Diphtheria</td>
<td><em>Corynebacterium diphtheriae</em></td>
<td>Pseudomembrane on throat, possibly leading to suffocation and death</td>
<td>Inhalation of respiratory droplets or aerosols from infected person</td>
<td>Identification of bacteria in throat swabs; PCR to detect diphtheria toxin in vitro</td>
<td>Erythromycin, penicillin, antitoxin produced in horses</td>
<td>DTP, DTaP</td>
</tr>
<tr>
<td>Legionnaires disease</td>
<td><em>Legionella pneumophila</em></td>
<td>Cough, fever, muscle aches, headaches, nausea, vomiting, confusion; sometimes fatal</td>
<td>Inhalation of aerosols from contaminated water reservoirs</td>
<td>Isolation, using Warthin-Starry procedure, of bacteria in sputum</td>
<td>Fluoroquinolones, macrolides</td>
<td>None</td>
</tr>
<tr>
<td>Pertussis (whooping cough)</td>
<td><em>Bordetella pertussis</em></td>
<td>Severe coughing with “whoop” sound; chronic cough lasting several months; can be fatal in infants</td>
<td>Inhalation of respiratory droplets from infected person</td>
<td>Direct culture of throat swab, PCR, ELISA</td>
<td>Macrolides</td>
<td>DTP, DTaP</td>
</tr>
<tr>
<td>Q fever</td>
<td><em>Coxiella burnetii</em></td>
<td>High fever, coughing, pneumonia, malaise; in chronic cases, potentially fatal endocarditis</td>
<td>Inhalation of aerosols of urine, feces, milk, or amniotic fluid of infected cattle, sheep, goats</td>
<td>PCR, ELISA</td>
<td>Doxycycline, hydroxychloroquine</td>
<td>None</td>
</tr>
<tr>
<td>Streptococcal pharyngitis, scarlet fever</td>
<td><em>Streptococcus pyogenes</em></td>
<td>Fever, sore throat, inflammation of pharynx and tonsils, pericardia, swollen lymph nodes; skin rash (scarlet fever), strawberry tongue</td>
<td>Direct contact, inhalation of respiratory droplets or aerosols from infected person</td>
<td>Direct culture of throat swab, rapid enzyme immunoassay</td>
<td>β-lactams</td>
<td>None</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td><em>Mycobacterium tuberculosis</em></td>
<td>Formation of tubercles in lungs; rupture of tubercles, leading to chronic, bloody cough; healed tubercles (Ghon complexes) visible in radiographs; can be fatal</td>
<td>Inhalation of respiratory droplets or aerosols from infected person</td>
<td>Mantoux tuberculin skin test with chest radiograph to identify Ghon complexes</td>
<td>Isoniazid, rifampin, ethambutol, pyrazinamide</td>
<td>BCG</td>
</tr>
</tbody>
</table>

---

**Figure 22.15**
## Bacterial Causes of Pneumonia

<table>
<thead>
<tr>
<th>Disease</th>
<th>Pathogen</th>
<th>Signs and Symptoms</th>
<th>Transmission</th>
<th>Diagnostic Tests</th>
<th>Antimicrobial Drugs</th>
<th>Vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlamydial pneumonia</td>
<td>Chlamydia phila pneumoniae, C. psittaci, Chlamydia trachomatis</td>
<td>Bronchitis; mid to severe respiratory distress</td>
<td>Inhalation of respiratory droplets or aerosols from infected person (C. pneumoniae); exposure to infected bird (C. psittaci); exposure in the birth canal (Chlamydia trachomatis)</td>
<td>Tissue culture, PCR</td>
<td>Tetracycline, macrolides</td>
<td>None</td>
</tr>
<tr>
<td>Haemophilus pneumonia</td>
<td>Haemophilus influenzae</td>
<td>Cough, fever or low body temperature, chills, chest pain, headache, fatigue</td>
<td>Inhalation of respiratory droplets or aerosols from infected person or asymptomatic carrier</td>
<td>Culture on chocolate agar, serotyping of blood or cerebrospinal fluid samples</td>
<td>Cephalosporins, fluoroquinolones</td>
<td>Hib</td>
</tr>
<tr>
<td>Klebsiella pneumonia</td>
<td>Klebsiella pneumoniae, others</td>
<td>Lung necrosis, “currant jelly” sputum; often fatal</td>
<td>Health care associated; bacteria introduced via contaminated ventilators, intubation, or other medical equipment</td>
<td>Culture, PCR</td>
<td>Multidrug resistant; antibiotic susceptibility testing necessary</td>
<td>None</td>
</tr>
<tr>
<td>Mycoplasma pneumonia (walking pneumonia)</td>
<td>Mycoplasma pneumoniae</td>
<td>Low fever, persistent cough</td>
<td>Inhalation of respiratory droplets or aerosols from infected person</td>
<td>Culture with penicillin, thallium acetate</td>
<td>Macrolides</td>
<td>None</td>
</tr>
<tr>
<td>Pneumococcal pneumonia</td>
<td>Streptococcus pneumoniae</td>
<td>Productive cough, bloody sputum, fever, chills, chest pain, respiratory distress</td>
<td>Direct contact with respiratory secretions</td>
<td>Gram stain, blood agar culture with optochin and sodium deoxycholate, quellung reaction</td>
<td>β-lactams, macrolides, fluoroquinolones</td>
<td>Pneumococcal conjugate vaccine (PCV13), pneumococcal polysaccharide vaccine (PPSV23)</td>
</tr>
<tr>
<td>Pseudomonas pneumonia</td>
<td>Pseudomonas aeruginosa</td>
<td>Viscous fluid and chronic inflammation of lungs; often fatal</td>
<td>Health care associated; bacteria introduced via contaminated ventilators; also frequently affects patients with cystic fibrosis</td>
<td>Culture from sputum or other body fluid</td>
<td>Multidrug resistant; antibiotic susceptibility testing necessary</td>
<td>None</td>
</tr>
</tbody>
</table>

Figure 22.16
22.3 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.\[^{[17]}\]

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.

Check Your Understanding

• How are colds transmitted?
• 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. [18]

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 22.2 compares the signs and symptoms of influenza and the common cold.

### Comparing the Common Cold and Influenza

<table>
<thead>
<tr>
<th>Sign/Symptom</th>
<th>Common Cold</th>
<th>Influenza</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>Low (37.2 °C [99 °F])</td>
<td>High (39 °C [102.2 °F])</td>
</tr>
<tr>
<td>Headache</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Aches and pains</td>
<td>Mild</td>
<td>Severe</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Slight</td>
<td>Severe</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Sneezing</td>
<td>Common</td>
<td>Rare</td>
</tr>
</tbody>
</table>

*Table 22.2*

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. [19]

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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 22.17. These spike proteins play important roles in the viral infectious cycle.

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 22.3. 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.

The Three Major Groups of Influenza Viruses

<table>
<thead>
<tr>
<th></th>
<th>Influenza A virus</th>
<th>Influenza B virus</th>
<th>Influenza C virus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severity</td>
<td>Severe</td>
<td>Moderate</td>
<td>Mild</td>
</tr>
</tbody>
</table>

Table 22.3

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 22.4.

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

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**Table 22.3**

<table>
<thead>
<tr>
<th></th>
<th>Influenza A virus</th>
<th>Influenza B virus</th>
<th>Influenza C virus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Animal reservoir</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Genome segments</td>
<td>8</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Population spread</td>
<td>Epidemic and pandemic</td>
<td>Epidemic</td>
<td>Sporadic</td>
</tr>
<tr>
<td>Antigenic variation</td>
<td>Shift/drift</td>
<td>Drift</td>
<td>Drift</td>
</tr>
</tbody>
</table>

**Table 22.4**

<table>
<thead>
<tr>
<th>Years</th>
<th>Common Name</th>
<th>Serotype</th>
<th>Estimated Number of Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>1918–1919</td>
<td>Spanish flu</td>
<td>H1N1</td>
<td>20,000,000–40,000,000</td>
</tr>
<tr>
<td>1957–1958</td>
<td>Asian flu</td>
<td>N2N2</td>
<td>1,000,000–2,000,000</td>
</tr>
<tr>
<td>1968–1969</td>
<td>Hong Kong flu</td>
<td>H3N2</td>
<td>1,000,000–3,000,000</td>
</tr>
<tr>
<td>2009–2010</td>
<td>Swine flu</td>
<td>H1N1/09</td>
<td>152,000–575,000</td>
</tr>
</tbody>
</table>

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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.[23] 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%.[24]

**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.

**Check Your Understanding**

- Compare the severity of the three types of influenza viruses.
- Why must new influenza vaccines be developed each year?

**Viral Pneumonia**

Viruses cause fewer cases of pneumonia than bacteria; however, several viruses can lead to pneumonia in children and the elderly. The most common sources of viral pneumonia are adenoviruses, influenza viruses, parainfluenza viruses, and respiratory syncytial viruses. The signs and symptoms produced by these viruses can range from mild cold-like

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symptoms to severe cases of pneumonia, depending on the virulence of the virus strain and the strength of the host defenses of the infected individual. Occasionally, infections can result in otitis media.

Respiratory syncytial virus (RSV) infections are fairly common in infants; most people have been infected by the age of 2 years. During infection, a viral surface protein causes host cells to fuse and form multinucleated giant cells called syncytia. There are no specific antiviral therapies or vaccines available for viral pneumonia. In adults, these infections are self-limiting, resemble the common cold, and tend to resolve unevenly within 1 or 2 weeks. Infections in infants, however, can be life-threatening. RSV is highly contagious and can be spread through respiratory droplets from coughing and sneezing. RSV can also survive for a long time on environmental surfaces and, thus, be transmitted indirectly via fomites.

Check Your Understanding

- Who is most likely to contract viral pneumonia?
- What is the recommended treatment for viral pneumonia?

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. 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.

Check Your Understanding

- What is the cause of SARS?
- What are the signs and symptoms of MERS?

Viral Respiratory Diseases Causing Skin Rashes

Measles, rubella (German measles), and chickenpox are three 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.

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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.\(^\text{[26]}\)

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 22.18).

![Figure 22.18](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.\(^\text{[27]}\)

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.\(^\text{[28]}\) When it is seen, it is often associated with children who have not been vaccinated.

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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. 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. Measles is highly communicable, and its spread at Disneyland may have been facilitated by the low vaccination rate in some communities in California.

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 22.19). 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. 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.

29. Ibid.
Chickenpox and Shingles

Chickenpox, also known as varicella, was once a common viral childhood disease. The causative agent of chickenpox, the varicella-zoster virus, is a member of the herpesvirus family. In children, the disease is mild and self-limiting, and is easily transmitted by direct contact or inhalation of material from the skin lesions. In adults, however, chickenpox infections can be much more severe and can lead to pneumonia and birth defects in the case of infected pregnant women. Reye syndrome, mentioned earlier in this chapter, is also a serious complication associated with chickenpox, generally in children.

Once infected, most individuals acquire a lifetime immunity to future chickenpox outbreaks. For this reason, parents once held “chickenpox parties” for their children. At these events, uninfected children were intentionally exposed to an infected individual so they would contract the disease earlier in life, when the incidence of complications is very low, rather than risk a more severe infection later.

After the initial viral exposure, chickenpox has an incubation period of about 2 weeks. The initial infection of the respiratory tract leads to viremia and eventually produces fever and chills. A pustular rash then develops on the face, progresses to the trunk, and then the extremities, although most form on the trunk (Figure 22.20). Eventually, the lesions burst and form a crusty scab. Individuals with chickenpox are infectious from about 2 days before the outbreak of the rash until all the lesions have scabbed over.
Like other herpesviruses, the varicella-zoster virus can become dormant in nerve cells. While the pustular vesicles are developing, the virus moves along sensory nerves to the dorsal ganglia in the spinal cord. Once there, the varicella-zoster virus can remain latent for decades. These dormant viruses may be reactivated later in life by a variety of stimuli, including stress, aging, and immunosuppression. Once reactivated, the virus moves along sensory nerves to the skin of the face or trunk. This results in the production of the painful lesions in a condition known as **shingles** (Figure 22.21). These symptoms generally last for 2–6 weeks, and may recur more than once. Postherpetic neuralgia, pain signals sent from damaged nerves long after the other symptoms have subsided, is also possible. In addition, the virus can spread to other organs in immunocompromised individuals. A person with shingles lesions can transmit the virus to a nonimmune contact, and the newly infected individual would develop chickenpox as the primary infection. Shingles cannot be transmitted from one person to another.

The primary diagnosis of chickenpox in children is mainly based on the presentation of a pustular rash of the trunk. Serological and PCR-based tests are available to confirm the initial diagnosis. Treatment for chickenpox infections in children is usually not required. In patients with shingles, acyclovir treatment can often reduce the severity and length of symptoms, and diminish the risk of postherpetic neuralgia. An effective vaccine is now available for chickenpox. A vaccine is also available for adults older than 60 years who were infected with chickenpox in their youth. This vaccine reduces the likelihood of a shingles outbreak by boosting the immune defenses that are keeping the latent infection in check and preventing reactivation.
Why does measles often lead to secondary infections?

What signs or symptoms would distinguish rubella and measles?

Why can chickenpox lead to shingles later in life?

Smallpox Stockpiles

Smallpox has probably killed more humans than any other infectious disease, with the possible exception of tuberculosis. This disease, caused by the variola major virus, is transmitted by inhalation of viral particles shed from lesions in the throat. The smallpox virus spreads systemically in the bloodstream and produces a pustular skin rash. Historical epidemics of smallpox had fatality rates of 50% or greater in susceptible populations. Concerted worldwide vaccination efforts eradicated smallpox from the general population in 1977. This was the first microbial disease in history to be eradicated, a feat made possible by the fact that the only reservoir for the smallpox virus is infected humans.

Although the virus is no longer present in the wild, laboratory samples of the virus still exist in the United States and Russia. The question is, why do these samples still exist? Some claim that these stocks should be maintained for research purposes. Should the smallpox virus ever reappear, they say, we would need access to such stocks for development of vaccines and treatments. Concerns about a re-emergence of the virus are not totally unfounded. Although there are no living reservoirs of the virus, there is always the possibility that smallpox could re-emerge from mummified human bodies or human remains preserved in permafrost. It is also possible that there are as-yet undiscovered samples of the virus in other locations around the world.
An example of such "lost" samples was discovered in a drawer in a Food and Drug Administration lab in Maryland.[34] If an outbreak from such a source were to occur, it could lead to uncontrolled epidemics, since the population is largely unvaccinated now.

Critics of this argument, including many research scientists and the World Health Organization, claim that there is no longer any rational argument for keeping the samples. They view the "re-emergence scenarios" as a thinly veiled pretense for harboring biological weapons. These scenarios, they say, are less probable than an intentional reintroduction of the virus from militarized stocks by humans. Furthermore, they point out that if we needed to research smallpox in the future, we could rebuild the virus from its DNA sequence.

What do you think? Are there legitimate arguments for maintaining stockpiles of smallpox, or should all forms of this deadly disease be eradicated?

Disease Profile

Viral Infections of the Respiratory Tract

Many viruses are capable of entering and causing disease in the respiratory system, and a number are able to spread beyond the respiratory system to cause systemic infections. Most of these infections are highly contagious and, with a few exceptions, antimicrobial drugs are not effective for treatment. Although some of these infections are self-limiting, others can have serious or fatal complications. Effective vaccines have been developed for several of these diseases, as summarized in Figure 22.22.

34. Ibid.
### Viral Infections of the Respiratory Tract

<table>
<thead>
<tr>
<th>Disease</th>
<th>Pathogen</th>
<th>Signs and Symptoms</th>
<th>Transmission</th>
<th>Vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chickenpox (varicella)</td>
<td>Varicella-zoster virus</td>
<td>In children, fever, chills, pustular rash of lesions that burst and form crusty scabs; in adults, more severe symptoms and complications (e.g., pneumonia)</td>
<td>Highly contagious via contact with aerosols, particles, or droplets from infected individual’s blisters or respiratory secretions</td>
<td>Varicella (chickenpox) vaccine</td>
</tr>
<tr>
<td>Common Cold</td>
<td>Rhinoviruses, adenoviruses, coronaviruses, others</td>
<td>Runny nose, congestion, sore throat, sneezing, headaches and muscle aches; may lead to otitis media, pharyngitis, laryngitis</td>
<td>Highly contagious via contact with respiratory secretions or inhalation of droplets or aerosols</td>
<td>None</td>
</tr>
<tr>
<td>Influenza</td>
<td>Influenza viruses A, B, C</td>
<td>Fever, chills, headaches, body aches, fatigue; may lead to pneumonia or complications such as Reye syndrome. Highly virulent strains may cause lethal complications</td>
<td>Highly contagious between humans via contact with respiratory secretions or inhalation of droplets or aerosols.</td>
<td>Vaccines developed yearly against most prevalent strains</td>
</tr>
<tr>
<td>Measles</td>
<td>Measles virus (MeV)</td>
<td>High fever, conjunctivitis, sore throat, macular rash becoming confluent, Koplik’s spots on oral mucosa; in severe cases, can lead to fatal pneumonia or encephalitis, especially in children</td>
<td>Highly contagious via contact with respiratory secretions, skin rash, or eye secretions of infected individual</td>
<td>MMR</td>
</tr>
<tr>
<td>MERS</td>
<td>Middle East respiratory syndrome coronavirus (MERS-CoV)</td>
<td>Fever, cough, shortness of breath; in some cases, complications such as pneumonia and kidney failure; can be fatal</td>
<td>Contact with respiratory secretions or inhalation of droplets or aerosols</td>
<td>None</td>
</tr>
<tr>
<td>Rubella (German measles)</td>
<td>Rubella virus</td>
<td>Facial rash spreading to extremities, followed by low-grade fever, headache, conjunctivitis, cough, runny nose, swollen lymph nodes; congenital rubella may cause birth defects, miscarriage, or stillbirth</td>
<td>Contagious via inhalation of droplets or aerosols from infected person or asymptomatic carrier; transplacental infection from mother to fetus</td>
<td>MMR</td>
</tr>
<tr>
<td>SARS</td>
<td>SARS-associated coronavirus (SARS-CoV)</td>
<td>High fever, headache, body aches, dry cough, pneumonia; can be fatal</td>
<td>Contact with respiratory secretions or inhalation of droplets or aerosols</td>
<td>None</td>
</tr>
<tr>
<td>Shingles</td>
<td>Varicella-zoster virus</td>
<td>Painful lesions on face or trunk lasting several weeks; may cause postherpetic neuralgia (chronic pain) or spread to organs in severe cases</td>
<td>Nontransmissible, occurs when dormant virus is reactivated, generally many years after initial chicken-pox infection</td>
<td>Herpes zoster (shingles) vaccine</td>
</tr>
<tr>
<td>Viral pneumonia</td>
<td>Adenoviruses, influenza viruses, parainfluenza viruses, respiratory syncytial viruses, others</td>
<td>From mild cold-like symptoms to severe pneumonia; in infants, RSV infections may be life-threatening</td>
<td>Highly contagious via contact with respiratory secretions or inhalation of droplets or aerosols</td>
<td>None</td>
</tr>
</tbody>
</table>
22.4 Respiratory Mycoses

Learning Objectives

• Identify the most common fungi that can cause infections of the respiratory tract
• Compare the major characteristics of specific fungal diseases of the respiratory tract

Fungal pathogens are ubiquitous in the environment. Serological studies have demonstrated that most people have been exposed to fungal respiratory pathogens during their lives. Yet symptomatic infections by these microbes are rare in healthy individuals. This demonstrates the efficacy of the defenses of our respiratory system. In this section, we will examine some of the fungi that can cause respiratory infections.

Histoplasmosis

Histoplasmosis is a fungal disease of the respiratory system and most commonly occurs in the Mississippi Valley of the United States and in parts of Central and South America, Africa, Asia, and Australia. The causative agent, *Histoplasma capsulatum*, is a dimorphic fungus. This microbe grows as a filamentous mold in the environment but occurs as a budding yeast during human infections. The primary reservoir for this pathogen is soil, particularly in locations rich in bat or bird feces.

Histoplasmosis is acquired by inhaling microconidial spores in the air; this disease is not transmitted from human to human. The incidence of histoplasmosis exposure is high in endemic areas, with 60%–90% of the population having anti-*Histoplasma* antibodies, depending on location; however, relatively few individuals exposed to the fungus actually experience symptoms. Those most likely to be affected are the very young, the elderly, and immunocompromised people.

In many ways, the course of this disease is similar to that of tuberculosis. Following inhalation, the spores enter the lungs and are phagocytized by alveolar macrophages. The fungal cells then survive and multiply within these phagocytes (see Figure 5.26). Focal infections cause the formation of granulomatous lesions, which can lead to calcifications that resemble the Ghon complexes of tuberculosis, even in asymptomatic cases. Also like tuberculosis, histoplasmosis can become chronic and reactivation can occur, along with dissemination to other areas of the body (e.g., the liver or spleen).

Signs and symptoms of pulmonary histoplasmosis include fever, headache, and weakness with some chest discomfort. The initial diagnosis is often based on chest radiographs and cultures grown on fungal selective media like Sabouraud's dextrose agar. Direct fluorescence antibody staining and Giemsa staining can also be used to detect this pathogen. In addition, serological tests including a complement fixation assay and histoplasmin sensitivity can be used to confirm the diagnosis. In most cases, these infections are self-limiting and antifungal therapy is not required. However, in disseminated disease, the antifungal agents amphotericin B and ketoconazole are effective; itraconazole may be effective in immunocompromised patients, in whom the disease can be more serious.

Check Your Understanding

• In what environments is one more likely to be infected with histoplasmosis?
• Identify at least two similarities between histoplasmosis and tuberculosis.

Coccidioidomycosis

Infection by the dimorphic fungus *Coccidioides immitis* causes coccidioidomycosis. Because the microbe is endemic to the San Joaquin Valley of California, the disease is sometimes referred to as Valley fever. A related species that

causes similar infections is found in semi-arid and arid regions of the southwestern United States, Mexico, and Central and South America.\(^{[36]}\)

Like histoplasmosis, coccidioidomycosis is acquired by inhaling fungal spores—in this case, arthrospores formed by hyphal fragmentation. Once in the body, the fungus differentiates into spherules that are filled with endospores. Most \(C.\ immitis\) infections are asymptomatic and self-limiting. However, the infection can be very serious for immunocompromised patients. The endospores may be transported in the blood, disseminating the infection and leading to the formation of granulomatous lesions on the face and nose (Figure 22.23). In severe cases, other major organs can become infected, leading to serious complications such as fatal meningitis.

Coccidioidomycosis can be diagnosed by culturing clinical samples. \(C.\ immitis\) readily grows on laboratory fungal media, such as Sabouraud's dextrose agar, at 35 °C (95 °F). Culturing the fungus, however, is rather dangerous. \(C.\ immitis\) is one of the most infectious fungal pathogens known and is capable of causing laboratory-acquired infections. Indeed, until 2012, this organism was considered a “select agent” of bioterrorism and classified as a BSL-3 microbe. Serological tests for antibody production are more often used for diagnosis. Although mild cases generally do not require intervention, disseminated infections can be treated with intravenous antifungal drugs like amphotericin B.

Figure 22.23  (a) This patient has extensive facial lesions due to a disseminated \(Coccidioides\) infection. (b) This fluorescent micrograph depicts a spherule of \(C.\ immitis\) containing endospores. (credit a, b: modification of work by Centers for Disease Control and Prevention)

**Clinical Focus**

**Resolution**

John’s negative RIDT tests do not rule out influenza, since false-negative results are common, but the \(Legionella\) infection still must be treated with antibiotic therapy and is the more serious condition. John’s prognosis is good, provided the physician can find an antibiotic therapy to which the infection responds.

While John was undergoing treatment, three of the employees from the home improvement store also reported to the clinic with very similar symptoms. All three were older than 55 years and had \(Legionella\) antigen in their urine; \(L.\ pneumophila\) was also isolated from their sputum. A team from the health department was sent to the home improvement store to identify a probable source for these infections. Their investigation revealed that about 3 weeks earlier, the store’s air conditioning system, which was located where the employees ate lunch,

had been undergoing maintenance. *L. pneumophila* was isolated from the cooling coils of the air conditioning system and intracellular *L. pneumophila* was observed in amoebae in samples of condensed water from the cooling coils as well (Figure 22.24). The amoebae provide protection for the *Legionella* bacteria and are known to enhance their pathogenicity.[37]

In the wake of the infections, the store ordered a comprehensive cleaning of the air conditioning system and implemented a regular maintenance program to prevent the growth of biofilms within the cooling tower. They also reviewed practices at their other facilities.

After a month of rest at home, John recovered from his infection enough to return to work, as did the other three employees of the store. However, John experienced lethargy and joint pain for more than a year after his treatment.

Figure 22.24  *Legionella pneumophila* (red intracellular rods) infecting amoebae from a contaminated water sample. (credit: modification of work by Centers for Disease Control and Prevention)

Go back to the previous Clinical Focus box.

**Blastomycosis**

Blastomycosis is a rare disease caused by another dimorphic fungus, *Blastomyces dermatitidis*. Like *Histoplasma* and *Coccidioides*, *Blastomyces* uses the soil as a reservoir, and fungal spores can be inhaled from disturbed soil. The pulmonary form of blastomycosis generally causes mild flu-like symptoms and is self-limiting. It can, however, become disseminated in immunocompromised people, leading to chronic cutaneous disease with subcutaneous lesions on the face and hands (Figure 22.25). These skin lesions eventually become crusty and discolored and can result in deforming scars. Systemic blastomycosis is rare, but if left untreated, it is always fatal.

Preliminary diagnosis of pulmonary blastomycosis can be made by observing the characteristic budding yeast forms in sputum samples. Commercially available urine antigen tests are now also available. Additional confirmatory tests include serological assays such as immunodiffusion tests or EIA. Most cases of blastomycosis respond well to amphotericin B or ketoconazole treatments.

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A variety of fungi in the order Mucorales cause mucormycosis, a rare fungal disease. These include bread molds, like Rhizopus and Mucor; the most commonly associated species is Rhizopus arrhizus (oryzae) (see Figure 5.28). These fungi can colonize many different tissues in immunocompromised patients, but often infect the skin, sinuses, or the lungs.

Although most people are regularly exposed to the causative agents of mucormycosis, infections in healthy individuals are rare. Exposure to spores from the environment typically occurs through inhalation, but the spores can also infect the skin through a wound or the gastrointestinal tract if ingested. Respiratory mucormycosis primarily affects immunocompromised individuals, such as patients with cancer or those who have had a transplant. After the spores are inhaled, the fungi grow by extending hyphae into the host’s tissues. Infections can occur in both the upper and lower respiratory tracts. Rhinocerebral mucormycosis is an infection of the sinuses and brain; symptoms include headache, fever, facial swelling, congestion, and tissue necrosis causing black lesions in the oral cavity. Pulmonary mucormycosis is an infection of the lungs; symptoms include fever, cough, chest pain, and shortness of

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Diagnosing mucormycosis can be challenging. Currently, there are no serological or PCR-based tests available to identify these infections. Tissue biopsy specimens must be examined for the presence of the fungal pathogens. The causative agents, however, are often difficult to distinguish from other filamentous fungi. Infections are typically treated by the intravenous administration of amphotericin B, and superficial infections are removed by surgical debridement. Since the patients are often immunocompromised, viral and bacterial secondary infections commonly develop. Mortality rates vary depending on the site of the infection, the causative fungus, and other factors, but a recent study found an overall mortality rate of 54\%.\footnote{MM Roden et al. “Epidemiology and Outcome of Zygomycosis: A Review of 929 Reported Cases.” \textit{Clinical Infectious Diseases} 41 no. 5 (2005):634–653.}

\begin{itemize}
\item Compare the modes of transmission for coccidioidomycosis, blastomycosis, and mucormycosis.
\item In general, which are more serious: the pulmonary or disseminated forms of these infections?
\end{itemize}

**Aspergillosis**

\textit{Aspergillus} is a common filamentous fungus found in soils and organic debris. Nearly everyone has been exposed to this mold, yet very few people become sick. In immunocompromised patients, however, \textit{Aspergillus} may become established and cause \textbf{aspergillosis}. Inhalation of spores can lead to asthma-like allergic reactions. The symptoms commonly include shortness of breath, wheezing, coughing, runny nose, and headaches. Fungal balls, or aspergilloma, can form when hyphal colonies collect in the lungs (\textit{Figure 22.26}). The fungal hyphae can invade the host tissues, leading to pulmonary hemorrhage and a bloody cough. In severe cases, the disease may progress to a disseminated form that is often fatal. Death most often results from pneumonia or brain hemorrhages.

Laboratory diagnosis typically requires chest radiographs and a microscopic examination of tissue and respiratory fluid samples. Serological tests are available to identify \textit{Aspergillus} antigens. In addition, a skin test can be performed to determine if the patient has been exposed to the fungus. This test is similar to the Mantoux tuberculin skin test used for tuberculosis. Aspergillosis is treated with intravenous antifungal agents, including itraconazole and voriconazole. Allergic symptoms can be managed with corticosteroids because these drugs suppress the immune system and reduce inflammation. However, in disseminated infections, corticosteroids must be discontinued to allow a protective immune response to occur.
Pneumocystis pneumonia

A type of pneumonia called Pneumocystis pneumonia (PCP) is caused by Pneumocystis jirovecii. Once thought to be a protozoan, this organism was formerly named P. carinii but it has been reclassified as a fungus and renamed based on biochemical and genetic analyses. Pneumocystis is a leading cause of pneumonia in patients with acquired immunodeficiency syndrome (AIDS) and can be seen in other compromised patients and premature infants. Respiratory infection leads to fever, cough, and shortness of breath. Diagnosis of these infections can be difficult. The organism is typically identified by microscopic examination of tissue and fluid samples from the lungs (Figure 22.27). A PCR-based test is available to detect P. jirovecii in asymptomatic patients with AIDS. The best treatment for these infections is the combination drug trimethoprim-sulfamethoxazole (TMP/SMZ). These sulfa drugs often have adverse effects, but the benefits outweigh these risks. Left untreated, PCP infections are often fatal.
Cryptococcosis

Infection by the encapsulated yeast Cryptococcus neoformans causes cryptococcosis. This fungus is ubiquitous in the soil and can be isolated from bird feces. Immunocompromised people are infected by inhaling basidiospores found in aerosols. The thick polysaccharide capsule surrounding these microbes enables them to avoid clearance by the alveolar macrophage. Initial symptoms of infection include fever, fatigue, and a dry cough. In immunocompromised patients, pulmonary infections often disseminate to the brain. The resulting meningitis produces headaches, sensitivity to light, and confusion. Left untreated, such infections are often fatal.

Cryptococcus infections are often diagnosed based on microscopic examination of lung tissues or cerebrospinal fluids. India ink preparations (Figure 22.28) can be used to visualize the extensive capsules that surround the yeast cells. Serological tests are also available to confirm the diagnosis. Amphotericin B, in combination with flucytosine, is typically used for the initial treatment of pulmonary infections. Amphotericin B is a broad-spectrum antifungal drug that targets fungal cell membranes. It can also adversely impact host cells and produce side effects. For this reason, clinicians must carefully balance the risks and benefits of treatments in these patients. Because it is difficult to eradicate cryptococcal infections, patients usually need to take fluconazole for up to 6 months after treatment with amphotericin B and flucytosine to clear the fungus. Cryptococcal infections are more common in immunocompromised people, such as those with AIDS. These patients typically require life-long suppressive therapy to control this fungal infection.

![Figure 22.28](credit a, b: modification of work by Centers for Disease Control and Prevention)

**Figure 22.28** (a) The micrograph shows stained budding Cryptococcus yeast cells from the lungs of a patient with AIDS. (b) The large capsule of Cryptococcus neoformans is visible in this negative stain micrograph. (credit a, b: modification of work by Centers for Disease Control and Prevention)

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**Check Your Understanding**

- What populations are most at risk for developing Pneumocystis pneumonia or cryptococcosis?
- Why are these infections fatal if left untreated?
Fungal Diseases of the Respiratory Tract

Most respiratory mycoses are caused by fungi that inhabit the environment. Such infections are generally transmitted via inhalation of fungal spores and cannot be transmitted between humans. In addition, healthy people are generally not susceptible to infection even when exposed; the fungi are only virulent enough to establish infection in patients with HIV, AIDS, or another condition that compromises the immune defenses. Figure 22.29 summarizes the features of important respiratory mycoses.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Pathogen</th>
<th>Signs and Symptoms</th>
<th>Diagnostic Tests</th>
<th>Antimicrobial Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspergillosis</td>
<td><em>Aspergillus fumigatus</em></td>
<td>Shortness of breath, wheezing, coughing, runny nose, headaches; formation of aspergilomas causing severe pneumonia and pulmonary or brain hemorrhages; can be fatal</td>
<td>Chest radiograph, skin test, microscopic observation of sputum samples</td>
<td>Itraconazole, voriconazole</td>
</tr>
<tr>
<td>Blastomycosis</td>
<td><em>Blastomyces dermatitidis</em></td>
<td>Fever, chills, cough, headache, fatigue, chest pain, body aches; in disseminated infections, chronic, crusted lesions on face and hands with permanent scarring; can be fatal</td>
<td>Microscopic observation of sputum samples; urine antigen test; EIA</td>
<td>Amphotericin B, ketoconazole</td>
</tr>
<tr>
<td>Coccioidioidomycosis (Valley fever)</td>
<td><em>Coccioides immitis</em></td>
<td>Granulomatous lesions on face and nose; may spread to organs or brain, causing fatal meningitis</td>
<td>Culture (in BSL-3 lab only), serological antibody tests</td>
<td>Amphotericin B</td>
</tr>
<tr>
<td>Cryptococcosis</td>
<td><em>Cryptococcus neoformans</em></td>
<td>Fever, cough, shortness of breath; can cause fatal meningitis if disseminated to brain</td>
<td>Microscopic examination of lung tissue or cerebrospinal fluid</td>
<td>Amphotericin B, fluconazole, flucytosine</td>
</tr>
<tr>
<td>Histoplasmosis</td>
<td><em>Histoplasma capsulatum</em></td>
<td>Fever, headache, weakness, chest pain, lesions on lungs</td>
<td>Chest radiograph, culture, direct fluorescence antibody staining, complement fixation assay, histoplasmin sensitivity test</td>
<td>Amphotericin B, ketoconazole, itraconazole</td>
</tr>
<tr>
<td>Mucormycosis</td>
<td><em>Rhizopus arrhizus</em>, other <em>Rhizopus spp.</em>, <em>Mucor spp.</em></td>
<td>Headache, fever, facial swelling, congestion, black lesions in oral cavity, cough, chest pain, shortness of breath; often fatal</td>
<td>Microscopic examination of tissue biopsy specimens</td>
<td>Amphotericin B</td>
</tr>
<tr>
<td>Pneumocystis pneumonia (PCP)</td>
<td><em>Pneumocystis jirovecii</em></td>
<td>Fever, cough, shortness of breath; can be fatal if untreated</td>
<td>Microscopic examination of lung tissue and fluid, PCR</td>
<td>Trimethoprim-sulfamethoxazole</td>
</tr>
</tbody>
</table>

Figure 22.29
Summary

22.1 Anatomy and Normal Microbiota of the Respiratory Tract

- The respiratory tract is divided into upper and lower regions at the epiglottis.
- Air enters the upper respiratory tract through the nasal cavity and mouth, which both lead to the pharynx. The lower respiratory tract extends from the larynx into the trachea before branching into the bronchi, which divide further to form the bronchioles, which terminate in alveoli, where gas exchange occurs.
- The upper respiratory tract is colonized by an extensive and diverse normal microbiota, many of which are potential pathogens. Few microbial inhabitants have been found in the lower respiratory tract, and these may be transients.
- Members of the normal microbiota may cause opportunistic infections, using a variety of strategies to overcome the innate nonspecific defenses (including the mucociliary escalator) and adaptive specific defenses of the respiratory system.
- Effective vaccines are available for many common respiratory pathogens, both bacterial and viral.
- Most respiratory infections result in inflammation of the infected tissues; these conditions are given names ending in -itis, such as rhinitis, sinusitis, otitis, pharyngitis, and bronchitis.

22.2 Bacterial Infections of the Respiratory Tract

- A wide variety of bacteria can cause respiratory diseases; most are treatable with antibiotics or preventable with vaccines.
- *Streptococcus pyogenes* causes strep throat, an infection of the pharynx that also causes high fever and can lead to scarlet fever, acute rheumatic fever, and acute glomerulonephritis.
- Acute otitis media is an infection of the middle ear that may be caused by several bacteria, including *Streptococcus pneumoniae, Haemophilus influenzae*, and *Moraxella catarrhalis*. The infection can block the eustachian tubes, leading to otitis media with effusion.
- Diphtheria, caused by *Corynebacterium diphtheriae*, is now a rare disease because of widespread vaccination. The bacteria produce exotoxins that kill cells in the pharynx, leading to the formation of a pseudomembrane; and damage other parts of the body.
- Bacterial pneumonia results from infections that cause inflammation and fluid accumulation in the alveoli. It is most commonly caused by *S. pneumoniae* or *H. influenzae*. The former is commonly multidrug resistant.
- Mycoplasma pneumonia results from infection by *Mycoplasma pneumoniae*; it can spread quickly, but the disease is mild and self-limiting.
- Chlamydial pneumonia can be caused by three pathogens that are obligate intracellular parasites. *Chlamydophila pneumoniae* is typically transmitted from an infected person, whereas *C. psittaci* is typically transmitted from an infected bird. *Chlamydia trachomatis*, may cause pneumonia in infants.
- Several other bacteria can cause pneumonia in immunocompromised individuals and those with cystic fibrosis.
- Tuberculosis is caused by *Mycobacterium tuberculosis*. Infection leads to the production of protective tubercles in the alveoli and calcified Ghon complexes that can harbor the bacteria for a long time. Antibiotic-resistant forms are common and treatment is typically long term.
- Pertussis is caused by *Bordetella pertussis*. Mucus accumulation in the lungs leads to prolonged severe coughing episodes (whooping cough) that facilitate transmission. Despite an available vaccine, outbreaks are still common.
- Legionnaires disease is caused by infection from environmental reservoirs of the *Legionella pneumophila* bacterium. The bacterium is endocytic within macrophages and infection can lead to pneumonia, particularly among immunocompromised individuals.
- Q fever is caused by *Coxiella burnetii*, whose primary hosts are domesticated mammals (zoonotic disease). It causes pneumonia primarily in farm workers and can lead to serious complications, such as endocarditis.
22.3 Viral Infections of the Respiratory Tract

- 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.
- Several viral infections, including **respiratory syncytial virus** infections, which frequently occur in the very young, can begin with mild symptoms before progressing to viral pneumonia.
- **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**, **rubella**, and **chickenpox** are highly contagious, systemic infections that gain entry through the respiratory system and cause rashes and fevers. Vaccines are available for all three. Measles is the most severe of the three and is responsible for significant mortality around the world. Chickenpox typically causes mild infections in children but the virus can reactivate to cause painful cases of **shingles** later in life.

22.4 Respiratory Mycoses

- Fungal pathogens rarely cause respiratory disease in healthy individuals, but inhalation of fungal spores can cause severe pneumonia and systemic infections in immunocompromised patients.
- Antifungal drugs like amphotericin B can control most fungal respiratory infections.
- **Histoplasmosis** is caused by a mold that grows in soil rich in bird or bat droppings. Few exposed individuals become sick, but vulnerable individuals are susceptible. The yeast-like infectious cells grow inside phagocytes.
- **Coccidioidomycosis** is also acquired from soil and, in some individuals, will cause lesions on the face. Extreme cases may infect other organs, causing death.
- **Blastomycosis**, a rare disease caused by a soil fungus, typically produces a mild lung infection but can become disseminated in the immunocompromised. Systemic cases are fatal if untreated.
- **Mucormycosis** is a rare disease, caused by fungi of the order Mucorales. It primarily affects immunocompromised people. Infection involves growth of the hyphae into infected tissues and can lead to death in some cases.
- **Aspergillosis**, caused by the common soil fungus *Aspergillus*, infects immunocompromised people. Hyphal balls may impede lung function and hyphal growth into tissues can cause damage. Disseminated forms can lead to death.
- **Pneumocystis pneumonia** is caused by the fungus *P. jirovecii*. The disease is found in patients with AIDS and other immunocompromised individuals. Sulfa drug treatments have side effects, but untreated cases may be fatal.
- **Cryptococcosis** is caused by *Cryptococcus neoformans*. Lung infections may move to the brain, causing meningitis, which can be fatal.

**Review Questions**

**Multiple Choice**

1. Which of the following is not directly connected to the nasopharynx?
   a. middle ear  
   b. oropharynx  
   c. lacrimal glands  
   d. nasal cavity

2. What type of cells produce the mucus for the mucous membranes?
   a. goblet cells  
   b. macrophages  
   c. phagocytes  
   d. ciliated epithelial cells
3. Which of these correctly orders the structures through which air passes during inhalation?
   a. pharynx → trachea → larynx → bronchi
   b. pharynx → larynx → trachea → bronchi
   c. larynx → pharynx → trachea → bronchi
   d. larynx → pharynx → trachea → bronchi

4. The ________ separates the upper and lower respiratory tract.
   a. bronchi
   b. larynx
   c. epiglottis
   d. palatine tonsil

5. Which microbial virulence factor is most important for attachment to host respiratory tissues?
   a. adhesins
   b. lipopolysaccharide
   c. hyaluronidase
   d. capsules

6. Which of the following does not involve a bacterial exotoxin?
   a. diphtheria
   b. whooping cough
   c. scarlet fever
   d. Q fever

7. What disease is caused by Coxiella burnetii?
   a. Q fever
   b. tuberculosis
   c. diphtheria
   d. walking pneumonia

8. In which stage of pertussis is the characteristic whooping sound made?
   a. convalescence
   b. catarrhal
   c. paroxysmal
   d. prodromal

9. What is the causative agent of Q fever?
   a. Coxiella burnetii
   b. Chlamydia psittaci
   c. Mycoplasma pneumoniae
   d. Streptococcus pyogenes

10. Which of these microbes causes “walking pneumonia”?
    a. Klebsiella pneumoniae
    b. Streptococcus pneumoniae
    c. Mycoplasma pneumoniae
    d. Chlamydia psittaci

11. Which of the following viruses is not commonly associated with the common cold?
    a. coronavirus
    b. adenovirus
    c. rhinovirus
    d. varicella-zoster virus

12. Which of the following viral diseases has been eliminated from the general population worldwide?
    a. smallpox
    b. measles
    c. German measles
    d. influenza

13. What term refers to multinucleated cells that form when many host cells fuse together during infections?
    a. Ghon elements
    b. Reye syndrome
    c. Koplik’s spots
    d. syncytia

14. 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

15. Which of these viruses is responsible for causing shingles?
    a. rubella virus
    b. measles virus
    c. varicella-zoster virus
    d. variola major virus

16. Which of these infections is also referred to as Valley fever?
    a. histoplasmosis
    b. coccidioidomycosis
    c. blastomycosis
    d. aspergillosis

17. Which of the following is not caused by a dimorphic fungus?
    a. histoplasmosis
    b. coccidioidomycosis
    c. blastomycosis
    d. aspergillosis

18. Which of the following is caused by infections by bread molds?
    a. mucormycosis
    b. coccidioidomycosis
    c. cryptococcosis
    d. Pneumocystis pneumonia
19. In the United States, most histoplasmosis cases occur
   a. in the Pacific northwest.
   b. in the desert southwest.
   c. in the Mississippi river valley.
   d. in Colorado river valley.

20. Which of the following infections can be diagnosed using a skin test similar to the tuberculin test?
   a. histoplasmosis
   b. cryptococcosis
   c. blastomycosis
   d. aspergillosis

**Fill in the Blank**

21. Unattached microbes are moved from the lungs to the epiglottis by the _______ effect.

22. Many bacterial pathogens produce _______ to evade phagocytosis.

23. The main type of antibody in the mucous membrane defenses is _______.

24. _______ results from an inflammation of the “voice box.”

25. _______ phagocytize potential pathogens in the lower lung.

26. Calcified lesions called _______ form in the lungs of patients with TB.

27. An inflammation of the middle ear is called _______.

28. The _______ is used to serologically identify *Streptococcus pneumoniae* isolates.

29. _______ is a zoonotic infection that can be contracted by people who handle birds.

30. The main virulence factor involved in scarlet fever is the _______.

31. The _______ virus is responsible for causing German measles.

32. A(n) _______ is an uncontrolled positive feedback loop between cytokines and leucocytes.

33. In cases of shingles, the antiviral drug _______ may be prescribed.

34. The slow accumulation of genetic changes to an influenza virus over time is referred to as _______.

35. The _______ vaccine is effective in controlling both measles and rubella.

36. In coccidioidomycosis, _______ containing many endospores form in the lungs.

37. In cryptococcosis, the main fungal virulence factor is the _______, which helps the pathogen avoid phagocytosis.

38. In some mycoses, fungal balls called _______ form in the lungs.

39. Most US cases of coccidioidomycosis occur in _______.

40. Coccidioidomycosis may develop when *Coccidioides immitis* _______ are inhaled.

**Short Answer**

41. Explain why the lower respiratory tract is essentially sterile.

42. Explain why pneumonia is often a life-threatening disease.

43. Name three bacteria that commonly cause pneumonia. Which is the most common cause?
44. How does smoking make an individual more susceptible to infections?
45. How does the diphtheria pathogen form a pseudomembrane?
46. Since we all have experienced many colds in our lifetime, why are we not resistant to future infections?
47. Which pulmonary fungal infection is most likely to be confused with tuberculosis? How can we discriminate between these two types of infection?
48. Compare and contrast aspergillosis and mucormycosis.

Critical Thinking
49. Name each of the structures of the respiratory tract shown, and state whether each has a relatively large or small normal microbiota.

Figure 22.30 (credit: modification of work by National Cancer Institute)

50. Cystic fibrosis causes, among other things, excess mucus to be formed in the lungs. The mucus is very dry and caked, unlike the moist, more-fluid mucus of normal lungs. What effect do you think that has on the lung’s defenses?
51. Why do you think smokers are more likely to suffer from respiratory tract infections?
52. Why might β-lactam antibiotics be ineffective against *Mycoplasma pneumoniae* infections?
53. Why is proper antibiotic therapy especially important for patients with tuberculosis?
54. What role does the common cold have in the rise of antibiotic-resistant strains of bacteria in the United States?
55. Why is it highly unlikely that influenza A virus will ever be eradicated, like the smallpox virus?
56. Why are fungal pulmonary infections rarely transmissible from person to person?
Chapter 23

Urogenital System Infections

Figure 23.1  Many pathogens that cause infections of the urogenital system can be detected in urine samples (left). The top sample in the culture (right) was prepared from the urine of a patient with a urinary tract infection. (credit b: modification of work by Nathan Reading)

Chapter Outline

23.1 Anatomy and Normal Microbiota of the Urogenital Tract
23.2 Bacterial Infections of the Urinary System
23.3 Bacterial Infections of the Reproductive System
23.4 Viral Infections of the Reproductive System
23.5 Fungal Infections of the Reproductive System
23.6 Protozoan Infections of the Urogenital System

Introduction

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.
23.1 Anatomy and Normal Microbiota of the Urogenital Tract

Learning Objectives
• Compare the anatomy, function, and normal microbiota associated with the male and female urogenital systems
• Explain how microorganisms, in general, overcome the defenses of the urogenital system to cause infection
• Name, describe, and differentiate between general signs and symptoms associated with infections of the urogenital tract

The urinary system filters blood, excretes wastes, and maintains an appropriate electrolyte and water balance. The reproductive system is responsible for the production of gametes and participates in conception and, in females, development of offspring. Due to their proximity and overlap, these systems are often studied together and referred to as the urogenital system (or genitourinary system).

Anatomy of the Urinary Tract

The basic structures of the urinary tract are common in males and females. However, there are unique locations for these structures in females and males, and there is a significant amount of overlap between the urinary and genital structures in males. Figure 23.2 illustrates the urinary anatomy common to females and males.

The kidneys carry out the urinary system’s primary functions of filtering the blood and maintaining water and electrolyte balance. The kidneys are composed of millions of filtration units called nephrons. Each nephron is in intimate contact with blood through a specialized capillary bed called the glomerulus (plural glomeruli). Fluids, electrolytes, and molecules from the blood pass from the glomerulus into the nephron, creating the filtrate that becomes urine (Figure 23.3). Urine that collects in each kidney empties through a ureter and drains to the urinary bladder, which stores urine. Urine is released from the bladder to the urethra, which transports it to be excreted from the body through the urinary meatus, the opening of the urethra.

Clinical Focus

Part 1

Nadia is a newly married 26-year-old graduate student in economics. Recently she has been experiencing an unusual vaginal discharge, as well as some itching and discomfort. Since she is due for her annual physical exam, she makes an appointment with her doctor hoping that her symptoms can be quickly treated. However, she worries that she may have some sort of sexually transmitted infection (STI). Although she is now in a monogamous relationship, she is not fully certain of her spouse’s sexual history and she is reluctant to ask him about it.

At her checkup, Nadia describes her symptoms to her primary care physician and, somewhat awkwardly, explains why she thinks she might have an STI. Nadia’s doctor reassures her that she regularly sees patients with similar concerns and encourages her to be fully transparent about her symptoms because some STIs can have serious complications if left untreated. After some further questioning, the doctor takes samples of Nadia’s blood, urine, and vaginal discharge to be sent to the lab for testing.

• What are some possible causes of Nadia’s symptoms?
• Why does the doctor take so many different samples?

Jump to the next Clinical Focus box.
Figure 23.2 These structures of the human urinary system are present in both males and females.

Figure 23.3 The kidney contains several lobes, each of which contains millions of nephrons. The nephron is the functional unit of the kidney, filtering the blood and removing water and dissolved compounds. The filtrate first enters the glomerulus and then enters the proximal convoluted tubule. As it passes through the tubule, the filtrate is further modified by osmosis and active transport until it reaches the larger ducts as urine.

Anatomy of the Reproductive System

The male reproductive system (Figure 23.4) is located in close proximity to the urinary system, and the urethra is part of both systems. The testes are responsible for the production of sperm. The epididymis is a coiled tube that collects sperm from the testes and passes it on to the vas deferens. The epididymis is also the site of sperm maturation after they leave the testes. The seminal vesicles and prostate are accessory glands that produce fluid that supports sperm. During ejaculation, the vas deferens releases this mixture of fluid and sperm, called semen, into the urethra, which extends to the end of the penis.

The female reproductive system is located near the urinary system (Figure 23.4). The external genitalia (vulva) in females open to the vagina, a muscular passageway that connects to the cervix. The cervix is the lower part of
the uterus (the organ where a fertilized egg will implant and develop). The cervix is a common site of infection, especially for viruses that may lead to cervical cancer. The uterus leads to the fallopian tubes and eventually to the ovaries. Ovaries are the site of ova (egg) production, as well as the site of estrogen and progesterone production that are involved in maturation and maintenance of reproductive organs, preparation of the uterus for pregnancy, and regulation of the menstrual cycle.

![Female reproductive system](image)

Figure 23.4 The female reproductive system is located in close proximity to the urinary system. In males, the urethra is shared by the reproductive and urinary systems.

Check Your Understanding

- What are the major structures of the urinary system, starting where urine is formed?
- What structure in males is shared by the reproductive and the urinary systems?

Normal Microbiota of the Urogenital System

The normal microbiota of different body sites provides an important nonspecific defense against infectious diseases (see Physical Defenses), and the urogenital tract is no exception. In both men and women, however, the kidneys are sterile. Although urine does contain some antibacterial components, bacteria will grow in urine left out at room temperature. Therefore, it is primarily the flushing action that keeps the ureters and bladder free of microbes.

Below the bladder, the normal microbiota of the male urogenital system is found primarily within the distal urethra and includes bacterial species that are commonly associated with the skin microbiota. In women, the normal microbiota is found within the distal one third of the urethra and the vagina. The normal microbiota of the vagina becomes established shortly after birth and is a complex and dynamic population of bacteria that fluctuates in response to environmental changes. Members of the vaginal microbiota play an important role in the nonspecific defense against vaginal infections and sexually transmitted infections by occupying cellular binding sites and competing for nutrients. In addition, the production of lactic acid by members of the microbiota provides an acidic environment within the vagina that also serves as a defense against infections. For the majority of women, the lactic-acid–producing bacteria in the vagina are dominated by a variety of species of Lactobacillus. For women who lack sufficient lactobacilli in their vagina, lactic acid production comes primarily from other species of bacteria such as Leptotrichia spp., Megasphaera spp., and Atopobium vaginae. Lactobacillus spp. use glycogen from vaginal epithelial cells for metabolism and production of lactic acid. This process is tightly regulated by the hormone estrogen. Increased levels of estrogen correlate with increased levels of vaginal glycogen, increased production of lactic acid, and a lower vaginal pH. Therefore, decreases in estrogen during the menstrual cycle and with menopause...
are associated with decreased levels of vaginal glycogen and lactic acid, and a higher pH. In addition to producing lactic acid, Lactobacillus spp. also contribute to the defenses against infectious disease through their production of hydrogen peroxide and bacteriocins (antibacterial peptides).

**Check Your Understanding**

- What factors affect the microbiota of the female reproductive tract?

**General Signs and Symptoms of Urogenital Infections**

Infections of the urinary tract most commonly cause inflammation of the bladder (cystitis) or of the urethra (urethritis). Urethritis can be associated with cystitis, but can also be caused by sexually transmitted infections. Symptoms of urethritis in men include burning sensation while urinating, discharge from the penis, and blood in the semen or the urine. In women, urethritis is associated with painful and frequent urination, vaginal discharge, fever, chills, and abdominal pain. The symptoms of cystitis are similar to those of urethritis. When urethritis is caused by a sexually transmitted pathogen, additional symptoms involving the genitalia can occur. These can include painful vesicles (blisters), warts, and ulcers. Ureteritis, a rare infection of the ureter, can also occur with cystitis. These infections can be acute or chronic.

Pyelonephritis and glomerulonephritis are infections of the kidney that are potentially serious. Pyelonephritis is an infection of one or both of the kidneys and may develop from a lower urinary tract infection; the upper urinary tract, including the ureters, is often affected. Signs and symptoms of pyelonephritis include fever, chills, nausea, vomiting, lower back pain, and frequent painful urination. Pyelonephritis usually only becomes chronic in individuals who have malformations in or damage to the kidneys.

Glomerulonephritis is an inflammation of the glomeruli of the nephrons. Symptoms include excessive protein and blood in urine, increased blood pressure, and fluid retention leading to edema of face, hands, and feet. Glomerulonephritis may be an acute infection or it can become chronic.

Infections occurring within the reproductive structures of males include epididymitis, orchitis, and prostatitis. Bacterial infections may cause inflammation of the epididymis, called epididymitis. This inflammation causes pain in the scrotum, testicles, and groin; swelling, redness, and warm skin in these areas may also be observed. Inflammation of the testicle, called orchitis, is usually caused by a bacterial infection spreading from the epididymis, but it can also be a complication of mumps, a viral disease. The symptoms are similar to those of epididymitis, and it is not uncommon for them both to occur together, in which case the condition is called epididymo-orchitis. Inflammation of the prostate gland, called prostatitis, can result from a bacterial infection. The signs and symptoms of prostatitis include fever, chills, and pain in the bladder, testicles, and penis. Patients may also experience burning during urination, difficulty emptying the bladder, and painful ejaculation.

Because of its proximity to the exterior, the vagina is a common site for infections in women. The general term for any inflammation of the vagina is vaginitis. Vaginitis often develops as a result of an overgrowth of bacteria or fungi that normally reside in the vaginal microbiota, although it can also result from infections by transient pathogens. Bacterial infections of the vagina are called bacterial vaginosis, whereas fungal infections (typically involving Candida spp.) are called yeast infections. Dynamic changes affecting the normal microbiota, acid production, and pH variations can be involved in the initiation of the microbial overgrowth and the development of vaginitis. Although some individuals may have no symptoms, vaginosis and vaginitis can be associated with discharge, odor, itching, and burning.

Pelvic inflammatory disease (PID) is an infection of the female reproductive organs including the uterus, cervix, fallopian tubes, and ovaries. The two most common pathogens are the sexually transmitted bacterial pathogens Neisseria gonorrhoeae and Chlamydia trachomatis. Inflammation of the fallopian tubes, called salpingitis, is the most serious form of PID. Symptoms of PID can vary between women and include pain in the lower abdomen, vaginal discharge, fever, chills, nausea, diarrhea, vomiting, and painful urination.
Check Your Understanding

- What conditions can result from infections affecting the urinary system?
- What are some common causes of vaginitis in women?

General Causes and Modes of Transmission of Urogenital Infections

Hormonal changes, particularly shifts in estrogen in women due to pregnancy or menopause, can increase susceptibility to urogenital infections. As discussed earlier, estrogen plays an important role in regulating the availability of glycogen and subsequent production of lactic acid by *Lactobacillus* species. Low levels of estrogen are associated with an increased vaginal pH and an increased risk of bacterial vaginosis and yeast infections. Estrogen also plays a role in maintaining the elasticity, strength, and thickness of the vaginal wall, and keeps the vaginal wall lubricated, reducing dryness. Low levels of estrogen are associated with thinning of the vaginal wall. This thinning increases the risk of tears and abrasions, which compromise the protective barrier and increase susceptibility to pathogens.

Another common cause of urogenital infections in females is fecal contamination that occurs because of the close proximity of the anus and the urethra. *Escherichia coli*, an important member of the digestive tract microbiota, is the most common cause of urinary tract infections (urethritis and cystitis) in women; it generally causes infection when it is introduced to the urethra in fecal matter. Good hygiene can reduce the risk of urinary tract infections by this route. In men, urinary tract infections are more commonly associated with other conditions, such as an enlarged prostate, kidney stones, or placement of a urinary catheter. All of these conditions impair the normal emptying of the bladder, which serves to flush out microbes capable of causing infection.

Infections that are transmitted between individuals through sexual contact are called sexually transmitted infections (STIs) or sexually transmitted diseases (STDs). (The CDC prefers the term STD, but WHO prefers STI, which encompasses infections that result in disease as well as those that are subclinical or asymptomatic.) STIs often affect the external genitalia and skin, where microbes are easily transferred through physical contact. Lymph nodes in the genital region may also become swollen as a result of infection. However, many STIs have systemic effects as well, causing symptoms that range from mild (e.g., general malaise) to severe (e.g., liver damage or serious immunosuppression).

Check Your Understanding

- What role does *Lactobacillus* play in the health of the female reproductive system?
- Why do urinary tract infections have different causes in males and females?

23.2 Bacterial Infections of the Urinary System

Learning Objectives

- Identify the most common bacterial pathogens that can cause urinary tract infections
- Compare the major characteristics of specific bacterial diseases affecting the urinary tract

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Urinary tract infections (UTIs) include infections of the urethra, bladder, and kidneys, and are common causes of urethritis, cystitis, pyelonephritis, and glomerulonephritis. Bacteria are the most common causes of UTIs, especially in the urethra and bladder.

**Cystitis**

Cystitis is most often caused by a bacterial infection of the bladder, but it can also occur as a reaction to certain treatments or irritants such as radiation treatment, hygiene sprays, or spermicides. Common symptoms of cystitis include **dysuria** (urination accompanied by burning, discomfort, or pain), **pyuria** (pus in the urine), **hematuria** (blood in the urine), and bladder pain.

In women, bladder infections are more common because the urethra is short and located in close proximity to the anus, which can result in infections of the urinary tract by fecal bacteria. Bladder infections are also more common in the elderly because the bladder may not empty fully, causing urine to pool; the elderly may also have weaker immune systems that make them more vulnerable to infection. Conditions such as prostatitis in men or kidney stones in both men and women can impact proper drainage of urine and increase risk of bladder infections. Catheterization can also increase the risk of bladder infection (see **Case in Point: Cystitis in the Elderly**).

Gram-negative bacteria such as *Escherichia coli* (most commonly), *Proteus vulgaris*, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae* cause most bladder infections. Gram-positive pathogens associated with cystitis include the coagulase-negative *Staphylococcus saprophyticus*, *Enterococcus faecalis*, and *Streptococcus agalactiae*. Routine manual urinalysis using a urine dipstick or test strip can be used for rapid screening of infection. These test strips (Figure 23.5) are either held in a urine stream or dipped in a sample of urine to test for the presence of nitrites, leukocyte esterase, protein, or blood that can indicate an active bacterial infection. The presence of nitrite may indicate the presence of *E. coli* or *K. pneumonia*; these bacteria produce nitrate reductase, which converts nitrate to nitrite. The leukocyte esterase (LE) test detects the presence of neutrophils as an indication of active infection.

Low specificity, sensitivity, or both, associated with these rapid screening tests require that care be taken in interpretation of results and in their use in diagnosis of urinary tract infections. Therefore, positive LE or nitrite results are followed by a urine culture to confirm a bladder infection. Urine culture is generally accomplished using blood agar and MacConkey agar, and it is important to culture a clean catch of urine to minimize contamination with normal microbiota of the penis and vagina. A clean catch of urine is accomplished by first washing the labia and urethral opening of female patients or the penis of male patients. The patient then releases a small amount of urine into the toilet bowl before stopping the flow of urine. Finally, the patient resumes urination, this time filling the container used to collect the specimen.

Bacterial cystitis is commonly treated with fluoroquinolones, nitrofurantoin, cephalosporins, or a combination of trimethoprim and sulfamethoxazole. Pain medications may provide relief for patients with dysuria. Treatment is more difficult in elderly patients, who experience a higher rate of complications such as sepsis and kidney infections.
Cystitis in the Elderly

Robert, an 81-year-old widower with early onset Alzheimer’s, was recently moved to a nursing home because he was having difficulty living on his own. Within a few weeks of his arrival, he developed a fever and began to experience pain associated with urination. He also began having episodes of confusion and delirium. The doctor assigned to examine Robert read his file and noticed that Robert was treated for prostatitis several years earlier. When he asked Robert how often he had been urinating, Robert explained that he had been trying not to drink too much so that he didn’t have to walk to the restroom.

All of this evidence suggests that Robert likely has a urinary tract infection. Robert’s age means that his immune system has probably begun to weaken, and his previous prostate condition may be making it difficult for him to empty his bladder. In addition, Robert’s avoidance of fluids has led to dehydration and infrequent urination, which may have allowed an infection to establish itself in his urinary tract. The fever and dysuria are common signs of a UTI in patients of all ages, and UTIs in elderly patients are often accompanied by a notable decline in mental function.

Physical challenges often discourage elderly individuals from urinating as frequently as they would otherwise. In addition, neurological conditions that disproportionately affect the elderly (e.g., Alzheimer’s and Parkinson’s disease) may also reduce their ability to empty their bladders. Robert’s doctor noted that he was having difficulty navigating his new home and recommended that he be given more assistance and that his fluid intake be monitored. The doctor also took a urine sample and ordered a laboratory culture to confirm the identity of the causative agent.

- Why is it important to identify the causative agent in a UTI?
- Should the doctor prescribe a broad-spectrum or narrow-spectrum antibiotic to treat Robert’s UTI? Why?
Kidney Infections (Pyelonephritis and Glomerulonephritis)

Pyelonephritis, an inflammation of the kidney, can be caused by bacteria that have spread from other parts of the urinary tract (such as the bladder). In addition, pyelonephritis can develop from bacteria that travel through the bloodstream to the kidney. When the infection spreads from the lower urinary tract, the causative agents are typically fecal bacteria such as *E. coli*. Common signs and symptoms include back pain (due to the location of the kidneys), fever, and nausea or vomiting. Gross hematuria (visible blood in the urine) occurs in 30–40% of women but is rare in men. The infection can become serious, potentially leading to bacteremia and systemic effects that can become life-threatening. Scarring of the kidney can occur and persist after the infection has cleared, which may lead to dysfunction.

Diagnosis of pyelonephritis is made using microscopic examination of urine, culture of urine, testing for leukocyte esterase and nitrite levels, and examination of the urine for blood or protein. It is also important to use blood cultures to evaluate the spread of the pathogen into the bloodstream. Imaging of the kidneys may be performed in high-risk patients with diabetes or immunosuppression, the elderly, patients with previous renal damage, or to rule out an obstruction in the kidney. Pyelonephritis can be treated with either oral or intravenous antibiotics, including penicillins, cephalosporins, vancomycin, fluoroquinolones, carbapenems, and aminoglycosides.

Glomerulonephritis occurs when the glomeruli of the nephrons are damaged from inflammation. Whereas pyelonephritis is usually acute, glomerulonephritis may be acute or chronic. The most well-characterized mechanism of glomerulonephritis is the post-streptococcal sequelae associated with *Streptococcus pyogenes* throat and skin infections. Although *S. pyogenes* does not directly infect the glomeruli of the kidney, immune complexes that form in blood between *S. pyogenes* antigens and antibodies lodge in the capillary endothelial cell junctions of the glomeruli and trigger a damaging inflammatory response. Glomerulonephritis can also occur in patients with bacterial endocarditis (infection and inflammation of heart tissue); however, it is currently unknown whether glomerulonephritis associated with endocarditis is also immune-mediated.

Leptospirosis

*Leptospira* are generally harmless spirochetes that are commonly found in the soil. However, some pathogenic species can cause an infection called leptospirosis in the kidneys and other organs (Figure 23.6). Leptospirosis can produce fever, headache, chills, vomiting, diarrhea, and rash with severe muscular pain. If the disease continues to progress, infection of the kidney, meninges, or liver may occur and may lead to organ failure or meningitis. When the kidney and liver become seriously infected, it is called Weil’s disease. Pulmonary hemorrhagic syndrome can also develop in the lungs, and jaundice may occur.

*Leptospira* spp. are found widely in animals such as dogs, horses, cattle, pigs, and rodents, and are excreted in their urine. Humans generally become infected by coming in contact with contaminated soil or water, often while swimming or during flooding; infection can also occur through contact with body fluids containing the bacteria. The bacteria may enter the body through mucous membranes, skin injuries, or by ingestion. The mechanism of pathogenicity is not well understood.

Leptospirosis is extremely rare in the United States, although it is endemic in Hawaii; 50% of all cases in the United States come from Hawaii. It is more common in tropical than in temperate climates, and individuals who work with animals or animal products are most at risk. The bacteria can also be cultivated in specialized media, with growth observed in broth in a few days to four weeks; however, diagnosis of leptospirosis is generally made using faster methods, such as detection of antibodies to *Leptospira* spp. in patient samples using serologic testing. Polymerase chain reaction (PCR), enzyme-linked immunosorbent assay (ELISA), slide agglutination, and indirect immunofluorescence tests may all be used for diagnosis. Treatment for leptospirosis involves broad-spectrum antibiotics such as penicillin and doxycycline. For more serious cases of leptospirosis, antibiotics may be given intravenously.


Figure 23.6  (a) Dark field view of Leptospira sp. (b) A scanning electron micrograph of Leptospira interrogans, a pathogenic species, shows the distinctive spirochete morphology of this genus. (credit b: modification of work by Janice Carr, Centers for Disease Control and Prevention)

Check Your Understanding

- What is the most common cause of a kidney infection?
- What are the most common symptoms of a kidney infection?

Nongonococcal Urethritis (NGU)

There are two main categories of bacterial urethritis: gonorrheal and nongonococcal. Gonorrheal urethritis is caused by Neisseria gonorrhoeae and is associated with gonorrhea, a common STI. This cause of urethritis will be discussed in Bacterial Infections of the Reproductive System. The term nongonococcal urethritis (NGU) refers to inflammation of the urethra that is unrelated to N. gonorrhoeae. In women, NGU is often asymptomatic. In men, NGU is typically a mild disease, but can lead to purulent discharge and dysuria. Because the symptoms are often mild or nonexistent, most infected individuals do not know that they are infected, yet they are carriers of the disease. Asymptomatic patients also have no reason to seek treatment, and although not common, untreated NGU can spread to the reproductive organs, causing pelvic inflammatory disease and salpingitis in women and epididymitis and prostatitis in men. Important bacterial pathogens that cause nongonococcal urethritis include Chlamydia trachomatis, Mycoplasma genitalium, Ureaplasma urealyticum, and Mycoplasma hominis.

C. trachomatis is a difficult-to-stain, gram-negative bacterium with an ovoid shape. An intracellular pathogen, C. trachomatis causes the most frequently reported STI in the United States, chlamydia. Although most persons infected with C. trachomatis are asymptomatic, some patients can present with NGU. C. trachomatis can also cause nongenital infections such as the ocular disease trachoma (see Bacterial Infections of the Skin and Eyes). The life cycle of C. trachomatis is illustrated in Figure 4.5.

C. trachomatis has multiple possible virulence factors that are currently being studied to evaluate their roles in causing disease. These include polymorphic outer-membrane autotransporter proteins, stress response proteins, and type III secretion effectors. The type III secretion effectors have been identified in gram-negative pathogens, including C. trachomatis. This virulence factor is an assembly of more than 20 proteins that form what is called an injectisome for the transfer of other effector proteins that target the infected host cells. The outer-membrane autotransporter proteins
are also an effective mechanism of delivering virulence factors involved in colonization, disease progression, and immune system evasion.

Other species associated with NGU include *Mycoplasma genitalium*, *Ureaplasma urealyticum*, and *Mycoplasma hominis*. These bacteria are commonly found in the normal microbiota of healthy individuals, who may acquire them during birth or through sexual contact, but they can sometimes cause infections leading to urethritis (in males and females) or vaginitis and cervicitis (in females).

*M. genitalium* is a more common cause of urethritis in most settings than *N. gonorrhoeae*, although it is less common than *C. trachomatis*. It is responsible for approximately 30% of recurrent or persistent infections, 20–25% of nonchlamydial NGU cases, and 15%–20% of NGU cases. *M. genitalium* attaches to epithelial cells and has substantial antigenic variation that helps it evade host immune responses. It has lipid-associated membrane proteins that are involved in causing inflammation.

Several possible virulence factors have been implicated in the pathogenesis of *U. urealyticum* (Figure 23.7). These include the ureaplasma proteins phospholipase A, phospholipase C, multiple banded antigen (MBA), urease, and immunoglobulin α protease. The phospholipases are virulence factors that damage the cytoplasmic membrane of target cells. The immunoglobulin α protease is an important defense against antibodies. It can generate hydrogen peroxide, which may adversely affect host cell membranes through the production of reactive oxygen species.

Treatments differ for gonorrheal and nongonococcal urethritis. However, *N. gonorrhoeae* and *C. trachomatis* are often simultaneously present, which is an important consideration for treatment. NGU is most commonly treated using tetracyclines (such as doxycycline) and azithromycin; erythromycin is an alternative option. Tetracyclines and fluoroquinolones are most commonly used to treat *U. urealyticum*, but resistance to tetracyclines is becoming an increasing problem. While tetracyclines have been the treatment of choice for *M. hominis*, increasing resistance means that other options must be used. Clindamycin and fluoroquinolones are alternatives. *M. genitalium* is generally susceptible to doxycycline, azithromycin, and moxifloxacin. Like other mycoplasma, *M. genitalium* does not have a cell wall and therefore β-lactams (including penicillins and cephalosporins) are not effective treatments.

![Figure 23.7](image)

*Figure 23.7*  *Ureaplasma urealyticum* microcolonies (white arrows) on agar surface after anaerobic incubation, visualized using phase contrast microscopy (800×). The black arrow indicates cellular debris. (credit: modification of work by American Society for Microbiology)

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### Check Your Understanding

- What are the three most common causes of urethritis?
- What three members of the normal microbiota can cause urethritis?

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Bacterial Infections of the Urinary Tract

Urinary tract infections can cause inflammation of the urethra (urethritis), bladder (cystitis), and kidneys (pyelonephritis), and can sometimes spread to other body systems through the bloodstream. Figure 23.8 captures the most important features of various types of UTIs.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Pathogen</th>
<th>Signs and Symptoms</th>
<th>Transmission</th>
<th>Diagnostic Tests</th>
<th>Antimicrobial Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystitis</td>
<td><em>Escherichia coli</em>, <em>Enterococcus faecalis</em>,</td>
<td>Dysuria, pyuria, hematuria, and bladder pain; most</td>
<td>Nontransmissible; opportunistic infections occur</td>
<td>Urine dipstick, urine culture for</td>
<td>Fluoroquinolones, nitrofurantoin, cephalosprins, trimethoprim, sulfamethoxazole</td>
</tr>
<tr>
<td></td>
<td><em>Streptococcus agalactiae</em>, *Klebsiella</td>
<td>common in females due to the shorter urethra and</td>
<td>when fecal bacteria are introduced to the</td>
<td>confirmation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>pneumoniae*, <em>Staphylococcus saprophyticus</em>,</td>
<td>abundant normal vaginal microbiota</td>
<td>urinary tract or when normal urination or</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>others</td>
<td></td>
<td>immune function is impaired</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leptospirosis</td>
<td><em>Leptospira</em> spp.</td>
<td>Fever, headache, chills, vomiting, diarrhea, rash,</td>
<td>From animals to humans via contact with urine or</td>
<td>PCR, ELISA, slide agglutination,</td>
<td>Doxycycline, amoxicillin, ampicillin,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>muscular pain; in disseminated infections, may cause</td>
<td>body fluids</td>
<td>indirect immunofluorescence</td>
<td>erythromycin, penicillin</td>
</tr>
<tr>
<td>Nongonococcal urethritis (NGU)</td>
<td><em>Chlamydia trachomatis</em>, *Mycoplasma</td>
<td>Mild or asymptomatic; may cause purulent discharge and</td>
<td>Transmitted sexually or from mother to neonate</td>
<td>Urethral swabs and urine culture, PCR,</td>
<td>Azithromycin, doxycycline, erythromycin,</td>
</tr>
<tr>
<td></td>
<td><em>genitalium</em>, <em>Mycoplasma hominis</em>, <em>Ureaplasma</em></td>
<td>dysuria</td>
<td>during birth</td>
<td>NAAT</td>
<td>fluoroquinolones</td>
</tr>
<tr>
<td>Pyelonephritis, glomerulone-</td>
<td><em>E. coli</em>, <em>Proteus</em> spp., *Klebsiella</td>
<td>Back pain, fever, nausea, vomiting, blood in urine;</td>
<td>Nontransmissible; infection spreads to</td>
<td>Uralysis, urine culture, radioimaging</td>
<td>Penicillins, cephalosprins, fluoroquinolones, aminoglycosides, others</td>
</tr>
<tr>
<td>phritis</td>
<td><em>spp.</em>, <em>Streptococcus pyogenes</em>, others</td>
<td>possible scarring of the kidneys and impaired kidney</td>
<td>kidneys from urinary tract or through</td>
<td>of kidneys</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>function; severe infections may lead to sepsis and</td>
<td>bloodstream</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Figure 23.8**
### 23.3 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.

#### Bacterial Vaginitis and Vaginosis

Inflammation of the vagina is called vaginitis, often caused by a bacterial infection. It is also possible to have an imbalance in the normal vaginal microbiota without inflammation called bacterial vaginosis (BV). Vaginosis may be asymptomatic or may cause mild symptoms such as a thin, white-to-yellow, homogeneous vaginal discharge, burning, odor, and itching. The major causative agent is *Gardnerella vaginalis*, a gram-variable to gram-negative pleomorphic bacterium. Other causative agents include anaerobic species such as members of the genera *Bacteroides* and *Fusobacterium*. Additionally, ureaplasma and mycoplasma may be involved. The disease is usually self-limiting, although antibiotic treatment is recommended if symptoms develop.

*G. vaginalis* appears to be more virulent than other vaginal bacterial species potentially associated with BV. Like *Lactobacillus* spp., *G. vaginalis* is part of the normal vaginal microbiota, but when the population of *Lactobacillus* spp. decreases and the vaginal pH increases, *G. vaginalis* flourishes, causing vaginosis by attaching to vaginal epithelial cells and forming a thick protective biofilm. *G. vaginalis* also produces a cytotoxin called vaginolysin that lyses vaginal epithelial cells and red blood cells.

Since *G. vaginalis* can also be isolated from healthy women, the “gold standard” for the diagnosis of BV is direct examination of vaginal secretions and not the culture of *G. vaginalis*. Diagnosis of bacterial vaginosis from vaginal secretions can be accurately made in three ways. The first is to use a DNA probe. The second method is to assay for sialidase activity (sialidase is an enzyme produced by *G. vaginalis* and other bacteria associated with vaginosis, including *Bacteroides* spp., *Prevotella* spp., and *Mobiluncus* spp.). The third method is to assess gram-stained vaginal smears for microscopic morphology and relative numbers and types of bacteria, squamous epithelial cells, and leukocytes. By examining slides prepared from vaginal swabs, it is possible to distinguish lactobacilli (long, gram-positive rods) from other gram-negative species responsible for BV. A shift in predominance from gram-positive bacilli to gram-negative coccobacilli can indicate BV. Additionally, the slide may contain so-called clue cells, which are epithelial cells that appear to have a granular or stippled appearance due to bacterial cells attached to their surface (Figure 23.9).

Presumptive diagnosis of bacterial vaginosis can involve an assessment of clinical symptoms and evaluation of vaginal fluids using Amsel’s diagnostic criteria which include 3 out of 4 of the following characteristics:

1. white to yellow discharge;
2. a fishy odor, most noticeable when 10% KOH is added;
3. pH greater than 4.5;
4. the presence of clue cells.

Treatment is often unnecessary because the infection often clears on its own. However, in some cases, antibiotics such as topical or oral clindamycin or metronidazole may be prescribed. Alternative treatments include oral tinidazole or clindamycin ovules (vaginal suppositories).
Figure 23.9 In this vaginal smear, the cell at the lower left is a clue cell with a unique appearance caused by the presence of bacteria on the cell. The cell on the right is a normal cell.

Check Your Understanding

- Explain the difference between vaginosis and vaginitis.
- What organisms are responsible for vaginosis and what organisms typically hold it at bay?

Clinical Focus

Part 2

There is no catch-all test for STIs, so several tests, in addition to a physical exam, are necessary to diagnose an infection. Nadia tries to relax in the exam room while she waits for the doctor to return, but she is nervous about the results.

When the doctor finally returns, she has some unexpected news: Nadia is pregnant. Surprised and excited, Nadia wants to know if the pregnancy explains her unusual symptoms. The doctor explains that the irritation that Nadia is experiencing is vaginitis, which can be caused by several types of microorganisms. One possibility is bacterial vaginosis, which develops when there is an imbalance in the bacteria in the vagina, as often occurs during pregnancy. Vaginosis can increase the risk of preterm birth and low birth weight, and a few studies have also shown that it can cause second-trimester miscarriage; however, the condition can be treated. To check for it, the doctor has asked the lab to perform a Gram stain on Nadia’s sample.

- What result would you expect from the Gram stain if Nadia has bacterial vaginosis?
• What is the relationship between pregnancy, estrogen levels, and development of bacterial vaginosis?

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

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 lipoooligosaccharide 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.

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 23.10). 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).

Figure 23.10  (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)

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 \textit{N. gonorrhoeae} can be difficult to treat due to antibiotic resistance (see Micro Connections). Some strains have developed resistance to the fluoroquinolones, so cephalosporins are often a first choice for treatment. Because co-infection with \textit{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.\footnote{Centers for Disease Control and Prevention. “2015 Sexually Transmitted Diseases Treatment Guidelines: Gonococcal Infections,” 2015. http://www.cdc.gov/std/tg2015/gonorrhea.htm.}

\begin{center}
\textbf{Check Your Understanding}
\end{center}

- What are some of the serious consequences of a gonorrhea infection?
- What organism commonly coinfects with \textit{N. gonorrhoeae}?

\begin{center}
\textbf{Micro Connections}
\end{center}

\textbf{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 \textit{Neisseria gonorrhoeae}. The CDC monitors the spread of antibiotic resistance in \textit{N. gonorrhoeae}, which it classifies as an urgent threat, and makes recommendations for treatment. So far, \textit{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 \textit{N. gonorrhoeae} that were resistant to at least one antibiotic.\footnote{Centers for Disease Control and Prevention. “Antibiotic Resistance Threats in the United States, 2013,” 2013. http://www.cdc.gov/drugresistance/pdf/ar-threats-2013-508.pdf.} 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 \textit{N. gonorrhoeae}.

\textbf{Chlamydia}

\textit{Chlamydia trachomatis} is the causative agent of the STI \textit{chlamydia} (Figure 23.11). While many \textit{Chlamydia} infections are asymptomatic, chlamydia is a major cause of nongonococcal urethritis (NGU) and may also cause epididymitis and orchitis in men. In women, chlamydia infections can cause urethritis, salpingitis, and PID. In addition, chlamydial infections may be associated with an increased risk of cervical cancer.

Because chlamydia is widespread, often asymptomatic, and has the potential to cause substantial complications, routine screening is recommended for sexually active women who are under age 25, at high risk (i.e., not in a monogamous relationship), or beginning prenatal care.
Certain serovars of *C. trachomatis* can cause an infection of the lymphatic system in the groin known as **lymphogranuloma venereum**. This condition is commonly found in tropical regions and can also co-occur in conjunction with human immunodeficiency virus (HIV) infection. After the microbes invade the lymphatic system, buboes (large lymph nodes, see **Figure 23.11**) form and can burst, releasing pus through the skin. The male genitals can become greatly enlarged and in women the rectum may become narrow.

Urogenital infections caused by *C. trachomatis* can be treated using azithromycin or doxycycline (the recommended regimen from the CDC). Erythromycin, levofloxacin, and ofloxacin are alternatives.

**Figure 23.11** (a) *Chlamydia trachomatis* inclusion bodies within McCoy cell monolayers. Inclusion bodies are distinguished by their brown color. (b) Lymphogranuloma venereum infection can cause swollen lymph nodes in the groin called buboes. (credit a: modification of work by Centers for Disease Control and Prevention; credit b: modification of work by Herbert L. Fred and Hendrik A. van Dijk)

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**Check Your Understanding**

- Compare the signs and symptoms of chlamydia infection in men and women.

**Syphilis**

**Syphilis** is spread through direct physical (generally sexual) contact, and is caused by the gram-negative spirochete *Treponema pallidum*. *T. pallidum* has a relatively simple genome and lacks lipopolysaccharide endotoxin characteristic of gram-negative bacteria. However, it does contain lipoproteins that trigger an immune response in the host, causing tissue damage that may enhance the pathogen’s ability to disseminate while evading the host immune system.

After entering the body, *T. pallidum* moves rapidly into the bloodstream and other tissues. If not treated effectively, syphilis progresses through three distinct stages: primary, secondary, and tertiary. Primary syphilis appears as a single lesion on the cervix, penis, or anus within 10 to 90 days of transmission. Such lesions contain many *T. pallidum* cells and are highly infectious. The lesion, called a **hard chancre**, is initially hard and painless, but it soon develops into an ulcerated sore (**Figure 23.12**). Localized lymph node swelling may occur as well. In some cases, these symptoms may be relatively mild, and the lesion may heal on its own within two to six weeks. Because the lesions are painless and often occur in hidden locations (e.g., the cervix or anus), infected individuals sometimes do not notice them.

The secondary stage generally develops once the primary chancre has healed or begun to heal. Secondary syphilis is characterized by a rash that affects the skin and mucous membranes of the mouth, vagina, or anus. The rash often begins on the palms or the soles of the feet and spreads to the trunk and the limbs (**Figure 23.12**). The rash may take many forms, such as macular or papular. On mucous membranes, it may manifest as mucus patches or white, wartlike lesions called **condylomata lata**. The rash may be accompanied by malaise, fever, and swelling of lymph.
nodes. Individuals are highly contagious in the secondary stage, which lasts two to six weeks and is recurrent in about 25% of cases.

After the secondary phase, syphilis can enter a latent phase, in which there are no symptoms but microbial levels remain high. Blood tests can still detect the disease during latency. The latent phase can persist for years.

Tertiary syphilis, which may occur 10 to 20 years after infection, produces the most severe symptoms and can be fatal. Granulomatous lesions called gummases may develop in a variety of locations, including mucous membranes, bones, and internal organs (Figure 23.12). Gummases can be large and destructive, potentially causing massive tissue damage. The most deadly lesions are those of the cardiovascular system (cardiovascular syphilis) and the central nervous system (neurosyphilis). Cardiovascular syphilis can result in a fatal aortic aneurysm (rupture of the aorta) or coronary stenosis (a blockage of the coronary artery). Damage to the central nervous system can cause dementia, personality changes, seizures, general paralysis, speech impairment, loss of vision and hearing, and loss of bowel and bladder control.

Figure 23.12  (a) This ulcerated sore is a hard chancre caused by syphilis. (b) This individual has a secondary syphilis rash on the hands. (c) Tertiary syphilis produces lesions called gummases, such as this one located on the nose. (credit a, b, c: modification of work by Centers for Disease Control and Prevention)

The recommended methods for diagnosing early syphilis are darkfield or brightfield (silver stain) microscopy of tissue or exudate from lesions to detect *T. pallidum* (Figure 23.13). If these methods are not available, two types of serologic tests (treponemal and nontreponemal) can be used for a presumptive diagnosis once the spirochete has spread in the body. Nontreponemal serologic tests include the Venereal Disease Research Laboratory (VDRL) and rapid plasma reagin (RPR) tests. These are similar screening tests that detect nonspecific antibodies (those for lipid antigens produced during infection) rather than those produced against the spirochete. Treponemal serologic tests measure antibodies directed against *T. pallidum* antigens using particle agglutination (*T. pallidum* passive particle agglutination or TP-PA), immunofluorescence (the fluorescent *T. pallidum* antibody absorption or FTA-ABS), various enzyme reactions (enzyme immunoassays or EIAs) and chemiluminescence immunoassays (CIA). Confirmatory testing, rather than screening, must be done using treponemal rather than nontreponemal tests because only the former tests for antibodies to spirochete antigens. Both treponemal and nontreponemal tests should be used (as opposed to just one) since both tests have limitations that can result in false positives or false negatives.

Neurosyphilis cannot be diagnosed using a single test. With or without clinical signs, it is generally necessary to assess a variety of factors, including reactive serologic test results, cerebrospinal fluid cell count abnormalities, cerebrospinal fluid protein abnormalities, or reactive VDRL-CSF (the VDRL test of cerebrospinal fluid). The VDRL-CSF is highly specific, but not sufficiently sensitive for conclusive diagnosis.

The recommended treatment for syphilis is parenteral penicillin G (especially long-acting benzathine penicillin, although the exact choice depends on the stage of disease). Other options include tetracycline and doxycycline.
Congenital Syphilis

Congenital syphilis is passed by mother to fetus when untreated primary or secondary syphilis is present. In many cases, infection may lead to miscarriage or stillbirth. Children born with congenital syphilis show symptoms of secondary syphilis and may develop mucus patches that deform the nose. In infants, gummas can cause significant tissue damage to organs and teeth. Many other complications may develop, such as osteochondritis, anemia, blindness, bone deformations, neurosyphilis, and cardiovascular lesions. Because congenital syphilis poses such a risk to the fetus, expectant mothers are screened for syphilis infection during the first trimester of pregnancy as part of the TORCH panel of prenatal tests.

Check Your Understanding

- What aspect of tertiary syphilis can lead to death?
- How do treponemal serologic tests detect an infection?

Chancroid

The sexually transmitted infection chancroid is caused by the gram-negative rod *Haemophilus ducreyi*. It is characterized by soft chancres (*Figure 23.14*) on the genitals or other areas associated with sexual contact, such as the mouth and anus. Unlike the hard chancres associated with syphilis, soft chancres develop into painful, open sores that may bleed or produce fluid that is highly contagious. In addition to causing chancres, the bacteria can invade the lymph nodes, potentially leading to pus discharge through the skin from lymph nodes in the groin. Like other genital lesions, soft chancres are of particular concern because they compromise the protective barriers of the skin or mucous membranes, making individuals more susceptible to HIV and other sexually transmitted diseases.

Several virulence factors have been associated with *H. ducreyi*, including lipooligosaccharides, protective outer membrane proteins, antiphagocytic proteins, secretory proteins, and collagen-specific adhesin NcaA. The collagen-specific adhesion NcaA plays an important role in initial cellular attachment and colonization. Outer membrane proteins DsrA and DltA have been shown to provide protection from serum-mediated killing by antibodies and complement.

*H. ducreyi* is difficult to culture; thus, diagnosis is generally based on clinical observation of genital ulcers and tests that rule out other diseases with similar ulcers, such as syphilis and genital herpes. PCR tests for *H. ducreyi* have been developed in some laboratories, but as of 2015 none had been cleared by the US Food and Drug Administration.
Recommended treatments for chancroid include antibiotics such as azithromycin, ciprofloxacin, erythromycin and ceftriaxone. Resistance to ciprofloxacin and erythromycin has been reported.

![a soft chancre on the penis of a man with chancroid](image1)
![gram-negative bacterium Haemophilus ducreyi](image2)

**Figure 23.14** (a) A soft chancre on the penis of a man with chancroid. (b) Chancroid is caused by the gram-negative bacterium *Haemophilus ducreyi*, seen here in a gram-stained culture of rabbit blood. (credit a, b: modification of work by Centers for Disease Control and Prevention)

**Check Your Understanding**

- What is the key difference between chancroid lesions and those associated with syphilis?
- Why is it difficult to definitively diagnose chancroid?

**Disease Profile**

**Bacterial Reproductive Tract Infections**

Many bacterial infections affecting the reproductive system are transmitted through sexual contact, but some can be transmitted by other means. In the United States, gonorrhea and chlamydia are common illnesses with incidences of about 350,000 and 1.44 million, respectively, in 2014. Syphilis is a rarer disease with an incidence of 20,000 in 2014. Chancroid is exceedingly rare in the United States with only six cases in 2014 and a median of 10 cases per year for the years 2010–2014. **Figure 23.15** summarizes bacterial infections of the reproductive tract.

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8. Ibid.
<table>
<thead>
<tr>
<th>Disease</th>
<th>Pathogen</th>
<th>Signs and Symptoms</th>
<th>Transmission</th>
<th>Diagnostic Tests</th>
<th>Antimicrobial Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial vaginosis (BV)</td>
<td>Gardnerella vaginalis, Bacteroides spp., Fusobacterium spp., others</td>
<td>Often asymptomatic; vaginal discharge, burning, odor, or itching</td>
<td>Opportunistic infection caused by imbalance of normal vaginal microbiota</td>
<td>Vaginal smear</td>
<td>Clindamycin, metronidazole, tinidazole</td>
</tr>
<tr>
<td>Chancroid</td>
<td>Haemophilus ducreyi</td>
<td>Soft, painful chancre on genitals, mouth, or anus; swollen lymph nodes; pus discharge</td>
<td>Sexual contact or contact with open lesions or discharge</td>
<td>Observation of clinical symptoms and negative tests for syphilis and herpes</td>
<td>Azithromycin, ceftriaxone, erythromycin, ciprofloxacin</td>
</tr>
<tr>
<td>Chlamydia</td>
<td>Chlamydia trachomatis</td>
<td>Often asymptomatic; in men, urethritis, epididymitis, orchitis; in women, urethritis, vaginal discharge or bleeding, pelvic inflammatory disease, salpingitis, increased risk of cervical cancer</td>
<td>Sexual contact or from mother to neonate during birth</td>
<td>NAAT, urine sample, vaginal swab, culture</td>
<td>Azithromycin, doxycycline, erythromycin, ofloxacin, levofloxacin</td>
</tr>
<tr>
<td>Gonorrhea</td>
<td>Neisseria gonorrhoeae</td>
<td>Urethritis, dysuria, penile or vaginal discharge, rectal pain and bleeding; in females, pelvic pain, intermenstrual bleeding, pelvic inflammatory disease, salpingitis, increased risk of infertility or ectopic pregnancy; in disseminated infections, arthritis, endocarditis, meningitis</td>
<td>Sexual contact</td>
<td>Urine sample or culture, NAAT, PCR, ELISA</td>
<td>Ceftriaxone, azithromycin</td>
</tr>
<tr>
<td>Syphilis</td>
<td>Treponema pallidum</td>
<td>Primary: hard chancre; Secondary: rash, cutaneous lesions, condyloma, malaise, fever, swollen lymph nodes; Tertiary: gummas, cardiovascular syphilis, neurosyphilis, possibly fatal</td>
<td>Sexual contact or from mother to neonate during birth</td>
<td>Darkfield or brightfield silver stain examination of lesion tissue or exudate, treponemal and non-treponemal serological testing, VDRL-CSF for neurosyphilis, prenatal TORCH panel</td>
<td>Penicillin G, tetracycline, doxycycline</td>
</tr>
</tbody>
</table>
23.4 Viral Infections of the Reproductive System

Learning Objectives

- Identify the most common viruses that cause infections of the reproductive system
- Compare the major characteristics of specific viral diseases affecting the reproductive system

Several viruses can cause serious problems for the human reproductive system. Most of these viral infections are incurable, increasing the risk of persistent sexual transmission. In addition, such viral infections are very common in the United States. For example, human papillomavirus (HPV) is the most common STI in the country, with an estimated prevalence of 79.1 million infections in 2008; herpes simplex virus 2 (HSV-2) is the next most prevalent STI at 24.1 million infections.\(^\text{10}\) In this section, we will examine these and other major viral infections of the reproductive system.

Genital Herpes

Genital herpes is a common condition caused by the herpes simplex virus (Figure 23.16), an enveloped, double-stranded DNA virus that is classified into two distinct types. Herpes simplex virus has several virulence factors, including infected cell protein (ICP) 34.5, which helps in replication and inhibits the maturation of dendritic cells as a mechanism of avoiding elimination by the immune system. In addition, surface glycoproteins on the viral envelope promote the coating of herpes simplex virus with antibodies and complement factors, allowing the virus to appear as “self” and prevent immune system activation and elimination.

There are two herpes simplex virus types. While herpes simplex virus type 1 (HSV-1) is generally associated with oral lesions like cold sores or fever blisters (see Viral Infections of the Skin and Eyes), herpes simplex virus type 2 (HSV-2) is usually associated with genital herpes. However, both viruses can infect either location as well as other parts of the body. Oral-genital contact can spread either virus from the mouth to the genital region or vice versa.

![Virions of the herpes simplex virus are shown here in this transmission electron micrograph. (credit: modification of work by Centers for Disease Control and Prevention)](image)

Many infected individuals do not develop symptoms, and thus do not realize that they carry the virus. However, in some infected individuals, fever, chills, malaise, swollen lymph nodes, and pain precede the development of fluid-filled vesicles that may be irritating and uncomfortable. When these vesicles burst, they release infectious fluid and allow transmission of HSV. In addition, open herpes lesions can increase the risk of spreading or acquiring HIV.

In men, the herpes lesions typically develop on the penis and may be accompanied by a watery discharge. In women, the vesicles develop most commonly on the vulva, but may also develop on the vagina or cervix (Figure 23.17).


This OpenStax book is available for free at http://cnx.org/content/col12087/1.4
The symptoms are typically mild, although the lesions may be irritating or accompanied by urinary discomfort. Use of condoms may not always be an effective means of preventing transmission of genital herpes since the lesions can occur on areas other than the genitals.

![Image of genital herpes lesions]

**Figure 23.17** Genital herpes is typically characterized by lesions on the genitals (left), but lesions can also appear elsewhere on the skin or mucous membranes (right). The lesions can be large and painful or small and easily overlooked. (credit b: modification of work by Schiffer JT, Swan D, Al Sallaq R, Magaret A, Johnston C, Mark KE, Selke S, Ocbarnichael N, Kuntz S, Zhu J, Robinson B, Huang ML, Jerome KR, Wald A, and Corey)

Herpes simplex viruses can cause recurrent infections because the virus can become latent and then be reactivated. This occurs more commonly with HSV-2 than with HSV-1. The virus moves down peripheral nerves, typically sensory neurons, to ganglia in the spine (either the trigeminal ganglion or the lumbar-sacral ganglia) and becomes latent. Reactivation can later occur, causing the formation of new vesicles. HSV-2 most effectively reactivates from the lumbar-sacral ganglia. Not everyone infected with HSV-2 experiences reactivations, which are typically associated with stressful conditions, and the frequency of reactivation varies throughout life and among individuals. Between outbreaks or when there are no obvious vesicles, the virus can still be transmitted.

Virologic and serologic techniques are used for diagnosis. The virus may be cultured from lesions. The immunostaining methods that are used to detect virus from cultures generally require less expertise than methods based on cytopathic effect (CPE), as well as being a less expensive option. However, PCR or other DNA amplification methods may be preferred because they provide the most rapid results without waiting for culture amplification. PCR is also best for detecting systemic infections. Serologic techniques are also useful in some circumstances, such as when symptoms persist but PCR testing is negative.

While there is no cure or vaccine for HSV-2 infections, antiviral medications are available that manage the infection by keeping the virus in its dormant or latent phase, reducing signs and symptoms. If the medication is discontinued, then the condition returns to its original severity. The recommended medications, which may be taken at the start of an outbreak or daily as a method of prophylaxis, are acyclovir, famciclovir, and valacyclovir.

**Neonatal Herpes**

Herpes infections in newborns, referred to as neonatal herpes, are generally transmitted from the mother to the neonate during childbirth, when the child is exposed to pathogens in the birth canal. Infections can occur regardless of whether lesions are present in the birth canal. In most cases, the infection of the newborn is limited to skin, mucous membranes, and eyes, and outcomes are good. However, sometimes the virus becomes disseminated and spreads to the central nervous system, resulting in motor function deficits or death.

In some cases, infections can occur before birth when the virus crosses the placenta. This can cause serious complications in fetal development and may result in spontaneous abortion or severe disabilities if the fetus survives. The condition is most serious when the mother is infected with HSV for the first time during pregnancy. Thus,

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expectant mothers are screened for HSV infection during the first trimester of pregnancy as part of the TORCH panel of prenatal tests (see How Pathogens Cause Disease). Systemic acyclovir treatment is recommended to treat newborns with neonatal herpes.

**Check Your Understanding**

- Why are latent herpes virus infections still of clinical concern?
- How is neonatal herpes contracted?

**Human Papillomomas**

Warts of all types are caused by a variety of strains of human papillomavirus (HPV) (see Viral Infections of the Skin and Eyes). Condylomata acuminata, more commonly called genital warts or venereal warts (Figure 23.18), are an extremely prevalent STI caused by certain strains of HPV. Condylomata are irregular, soft, pink growths that are found on external genitalia or the anus.

HPV is a small, non-enveloped virus with a circular double-stranded DNA genome. Researchers have identified over 200 different strains (called types) of HPV, with approximately 40 causing STIs. While some types of HPV cause genital warts, HPV infection is often asymptomatic and self-limiting. However, genital HPV infection often co-occurs with other STIs like syphilis or gonorrhea. Additionally, some forms of HPV (not the same ones associated with genital warts) are associated with cervical cancers. At least 14 oncogenic (cancer-causing) HPV types are known to have a causal association with cervical cancers. Examples of oncogenic HPV are types 16 and 18, which are associated with 70% of cervical cancers. Oncogenic HPV types can also cause oropharyngeal cancer, anal cancer, vaginal cancer, vulvar cancer, and penile cancer. Most of these cancers are caused by HPV type 16. HPV virulence factors include proteins (E6 and E7) that are capable of inactivating tumor suppressor proteins, leading to uncontrolled cell division and the development of cancer.

HPV cannot be cultured, so molecular tests are the primary method used to detect HPV. While routine HPV screening is not recommended for men, it is included in guidelines for women. An initial screening for HPV at age 30, conducted at the same time as a Pap test, is recommended. If the tests are negative, then further HPV testing is recommended every five years. More frequent testing may be needed in some cases. The protocols used to collect, transport, and store samples vary based on both the type of HPV testing and the purpose of the testing. This should be determined in individual cases in consultation with the laboratory that will perform the testing.

Because HPV testing is often conducted concurrently with Pap testing, the most common approach uses a single sample collection within one vial for both. This approach uses liquid-based cytology (LBC). The samples are then used for Pap smear cytology as well as HPV testing and genotyping. HPV can be recognized in Pap smears by the presence of cells called koilocytes (called koilocytosis or koilocytotic atypia). Koilocytes have a hyperchromatic atypical nucleus that stains darkly and a high ratio of nuclear material to cytoplasm. There is a distinct clear appearance around the nucleus called a perinuclear halo (Figure 23.19).

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Most HPV infections resolve spontaneously; however, various therapies are used to treat and remove warts. Topical medications such as imiquimod (which stimulates the production of interferon), podofilox, or sinecatechins, may be effective. Warts can also be removed using cryotherapy or surgery, but these approaches are less effective for genital warts than for other types of warts. Electrocauterization and carbon dioxide laser therapy are also used for wart removal.

Regular Pap testing can detect abnormal cells that might progress to cervical cancer, followed by biopsy and appropriate treatment. Vaccines for some of the high risk HPV types are now available. Gardasil vaccine includes types 6, 11, 16 and 18 (types 6 and 11 are associated with 90% of genital wart infections and types 16 and 18 are associated with 70% of cervical cancers). Gardasil 9 vaccinates against the previous four types and an additional five high-risk types (31, 33, 45, 52, and 58). Cervarix vaccine includes just HPV types 16 and 18. Vaccination is the most effective way to prevent infection with oncogenic HPV, but it is important to note that not all oncogenic HPV types are covered by the available vaccines. It is recommended for both boys and girls prior to sexual activity (usually between the ages of nine and fifteen).
Watch a video (https://openstax.org/l/22HPVpercep) of how perceptions of HPV affect vaccination rates.

**Check Your Understanding**

- What is diagnostic of an HPV infection in a Pap smear?
- What is the motivation for HPV vaccination?

**Secret STIs**

Few people who have an STI (or think they may have one) are eager to share that information publicly. In fact, many patients are even uncomfortable discussing the symptoms privately with their doctors. Unfortunately, the social stigma associated with STIs makes it harder for infected individuals to seek the treatment they need and creates the false perception that STIs are rare. In reality, STIs are quite common, but it is difficult to determine exactly how common.

A recent study on the effects of HPV vaccination found a baseline HPV prevalence of 26.8% for women between the ages of 14 and 59. Among women aged 20–24, the prevalence was 44.8%; in other words, almost half of the women in this age bracket had a current infection. According to the CDC, HSV-2 infection was estimated to have a prevalence of 15.5% in younger individuals (14–49 years of age) in 2007–2010, down from 20.3% in the same age group in 1988–1994. However, the CDC estimates that 87.4% of infected individuals in this age group have not been diagnosed by a physician.

Another complicating factor is that many STIs can be asymptomatic or have long periods of latency. For example, the CDC estimates that among women ages 14–49 in the United States, about 2.3 million (3.1%) are infected with the sexually transmitted protozoan *Trichomonas* (see Protozoan Infections of the Urogenital System); however, in a study of infected women, 85% of those diagnosed with the infection were asymptomatic.

Even when patients are treated for symptomatic STIs, it can be difficult to obtain accurate data on the number of cases. Whereas STIs like chlamydia, gonorrhea, and syphilis are notifiable diseases—meaning each diagnosis must be reported by healthcare providers to the CDC—other STIs are not notifiable (e.g., genital herpes, genital warts, and trichomoniasis). Between the social taboos, the inconsistency of symptoms, and the lack of mandatory reporting, it can be difficult to estimate the true prevalence of STIs—but it is safe to say they are much more prevalent than most people think.

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Viral Reproductive Tract Infections

Figure 23.20 summarizes the most important features of viral diseases affecting the human reproductive tract.

<table>
<thead>
<tr>
<th>Viral Infections of the Reproductive Tract</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Disease</strong></td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>Cervical cancer</td>
</tr>
<tr>
<td>Genital herpes</td>
</tr>
<tr>
<td>Human papillomas</td>
</tr>
<tr>
<td>Neonatal herpes</td>
</tr>
</tbody>
</table>

23.5 Fungal Infections of the Reproductive System

Learning Objectives

- Summarize the important characteristics of vaginal candidiasis

Only one major fungal pathogen affects the urogenital system. *Candida* is a genus of fungi capable of existing in a yeast form or as a multicellular fungus. *Candida* spp. are commonly found in the normal, healthy microbiota of the skin, gastrointestinal tract, respiratory system, and female urogenital tract (Figure 23.21). They can be pathogenic due to their ability to adhere to and invade host cells, form biofilms, secrete hydrolases (e.g., proteases, phospholipases, and lipases) that assist in their spread through tissues, and change their phenotypes to protect themselves from the immune system. However, they typically only cause disease in the female reproductive tract under conditions that compromise the host’s defenses. While there are at least 20 *Candida* species of clinical importance, *C. albicans* is the species most commonly responsible for fungal vaginitis.
As discussed earlier, lactobacilli in the vagina inhibit the growth of other organisms, including bacteria and *Candida*, but disruptions can allow *Candida* to increase in numbers. Typical disruptions include antibiotic therapy, illness (especially diabetes), pregnancy, and the presence of transient microbes. Immunosuppression can also play a role, and the severe immunosuppression associated with HIV infection often allows *Candida* to thrive. This can cause genital or vaginal candidiasis, a condition characterized by vaginitis and commonly known as a yeast infection. When a yeast infection develops, inflammation occurs along with symptoms of pruritus (itching), a thick white or yellow discharge, and odor.

Other forms of candidiasis include cutaneous candidiasis (see *Mycoses of the Skin*) and oral thrush (see *Microbial Diseases of the Mouth and Oral Cavity*). Although *Candida* spp. are found in the normal microbiota, *Candida* spp. may also be transmitted between individuals. Sexual contact is a common mode of transmission, although candidiasis is not considered an STI.

Diagnosis of vaginal candidiasis can be made using microscopic evaluation of vaginal secretions to determine whether there is an excess of *Candida*. Culturing approaches are less useful because *Candida* is part of the normal microbiota and will regularly appear. It is also easy to contaminate samples with *Candida* because it is so common, so care must be taken to handle clinical material appropriately. Samples can be refrigerated if there is a delay in handling. *Candida* is a dimorphic fungus, so it does not only exist in a yeast form; cultivation can be used to identify chlamydospores and pseudohyphae, which develop from germ tubes (Figure 23.22). The presence of the germ tube can be used in a diagnostic test in which cultured yeast cells are combined with rabbit serum and observed after a few hours for the presence of germ tubes. Molecular tests are also available if needed. The Affirm VPII Microbial Identification Test, for instance, tests simultaneously for the vaginal microbes *C. albicans*, *G. vaginalis* (see *Bacterial Infections of the Urinary System*), and *Trichomonas vaginalis* (see *Protozoan Infections of the Urogenital System*).

Topical antifungal medications for vaginal candidiasis include butoconazole, miconazole, clotrimazole, tioconazole, and nystatin. Oral treatment with fluconazole can be used. There are often no clear precipitating factors for infection, so prevention is difficult.

![Figure 23.21](https://example.com/image.png) Figure 23.21  *Candida* blastospores (asexual spores that result from budding) and chlamydospores (resting spores produced through asexual reproduction) are visible in this micrograph. (credit: modification of work by Centers for Disease Control and Prevention)
Figure 23.22  *Candida* can produce germ tubes, like the one in this micrograph, that develop into hyphae. (credit: modification of work by American Society for Microbiology)

**Check Your Understanding**

- What factors can lead to candidiasis?
- How is candidiasis typically diagnosed?

**Clinical Focus**

**Part 3**

The Gram stain of Nadia’s vaginal smear showed that the concentration of lactobacilli relative to other species in Nadia’s vaginal sample was abnormally low. However, there were no clue cells visible, which suggests that the infection is not bacterial vaginosis. But a wet-mount slide showed an overgrowth of yeast cells, suggesting that the problem is candidiasis, or a yeast infection (*Figure 23.23*). This, Nadia’s doctor assures her, is good news. Candidiasis is common during pregnancy and easily treatable.

- Knowing that the problem is candidiasis, what treatments might the doctor suggest?
23.6 Protozoan Infections of the Urogenital System

Learning Objectives

- Identify the most common protozoan pathogen that causes infections of the reproductive system
- Summarize the important characteristics of trichomoniasis

Only one major protozoan species causes infections in the urogenital system. **Trichomoniasis**, or “trich,” is the most common nonviral STI and is caused by a flagellated protozoan *Trichomonas vaginalis*. *T. vaginalis* has an undulating membrane and, generally, an amoeboid shape when attached to cells in the vagina. In culture, it has an oval shape.

*T. vaginalis* is commonly found in the normal microbiota of the vagina. As with other vaginal pathogens, it can cause vaginitis when there is disruption to the normal microbiota. It is found only as a trophozoite and does not form cysts. *T. vaginalis* can adhere to cells using adhesins such as lipoglycans; it also has other cell-surface virulence factors, including tetraspanins that are involved in cell adhesion, motility, and tissue invasion. In addition, *T. vaginalis* is capable of phagocytosing other microbes of the normal microbiota, contributing to the development of an imbalance that is favorable to infection.

Both men and women can develop trichomoniasis. Men are generally asymptomatic, and although women are more likely to develop symptoms, they are often asymptomatic as well. When symptoms do occur, they are characteristic of urethritis. Men experience itching, irritation, discharge from the penis, and burning after urination or ejaculation. Women experience dysuria; itching, burning, redness, and soreness of the genitalia; and vaginal discharge. The infection may also spread to the cervix. Infection increases the risk of transmitting or acquiring HIV and is associated with pregnancy complications such as preterm birth.

Microscopic evaluation of wet mounts is an inexpensive and convenient method of diagnosis, but the sensitivity of this method is low (**Figure 23.24**). Nucleic acid amplification testing (NAAT) is preferred due to its high sensitivity. Using wet mounts and then NAAT for those who initially test negative is one option to improve sensitivity.
Samples may be obtained for NAAT using urine, vaginal, or endocervical specimens for women and with urine and urethral swabs for men. It is also possible to use other methods such as the OSOM Trichomonas Rapid Test (an immunochromatographic test that detects antigen) and a DNA probe test for multiple species associated with vaginitis (the Affirm VPII Microbial Identification Test discussed in section 23.5).\(^{[16]}\) *T. vaginalis* is sometimes detected on a Pap test, but this is not considered diagnostic due to high rates of false positives and negatives. The recommended treatment for trichomoniasis is oral metronidazole or tinidazole. Sexual partners should be treated as well.

![Image of T. vaginalis](credit: modification of work by American Society for Microbiology)

**Figure 23.24** *Trichomonas vaginalis* is visible in this Gram stained specimen. (credit: modification of work by American Society for Microbiology)

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**Check Your Understanding**

- What are the symptoms of trichomoniasis?

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**Eye on Ethics**

**STIs and Privacy**

For many STIs, it is common to contact and treat sexual partners of the patient. This is especially important when a new illness has appeared, as when HIV became more prevalent in the 1980s. But to contact sexual partners, it is necessary to obtain their personal information from the patient. This raises difficult questions. In some cases, providing the information may be embarrassing or difficult for the patient, even though withholding such information could put their sexual partner(s) at risk.

Legal considerations further complicate such situations. The Health Insurance Portability and Accountability Act (HIPPA), passed into law in 1996, sets the standards for the protection of patient information. It requires businesses that use health information, such as insurance companies and healthcare providers, to maintain strict confidentiality of patient records. Contacting a patient’s sexual partners may therefore violate the patient’s privacy rights if the patient’s diagnosis is revealed as a result.

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From an ethical standpoint, which is more important: the patient's privacy rights or the sexual partner’s right to know that they may be at risk of a sexually transmitted disease? Does the answer depend on the severity of the disease or are the rules universal? Suppose the physician knows the identity of the sexual partner but the patient does not want that individual to be contacted. Would it be a violation of HIPPA rules to contact the individual without the patient’s consent?

Questions related to patient privacy become even more complicated when dealing with patients who are minors. Adolescents may be reluctant to discuss their sexual behavior or health with a health professional, especially if they believe that healthcare professionals will tell their parents. This leaves many teens at risk of having an untreated infection or of lacking the information to protect themselves and their partners. On the other hand, parents may feel that they have a right to know what is going on with their child. How should physicians handle this? Should parents always be told even if the adolescent wants confidentiality? Does this affect how the physician should handle notifying a sexual partner?

Resolution

Vaginal candidiasis is generally treated using topical antifungal medications such as butoconazole, miconazole, clotrimazole, ticonozole, nystatin, or oral fluconazole. However, it is important to be careful in selecting a treatment for use during pregnancy. Nadia’s doctor recommended treatment with topical clotrimazole. This drug is classified as a category B drug by the FDA for use in pregnancy, and there appears to be no evidence of harm, at least in the second or third trimesters of pregnancy. Based on Nadia’s particular situation, her doctor thought that it was suitable for very short-term use even though she was still in the first trimester. After a seven-day course of treatment, Nadia’s yeast infection cleared. She continued with a normal pregnancy and delivered a healthy baby eight months later.

Higher levels of hormones during pregnancy can shift the typical microbiota composition and balance in the vagina, leading to high rates of infections such as candidiasis or vaginosis. Topical treatment has an 80–90% success rate, with only a small number of cases resulting in recurrent or persistent infections. Longer term or intermittent treatment is usually effective in these cases.

Go back to the previous Clinical Focus box.

Disease Profile

Fungal and Protozoan Reproductive Tract Infections

Figure 23.25 summarizes the most important features of candidiasis and trichomoniais.
Summary

23.1 Anatomy and Normal Microbiota of the Urogenital Tract

- The urinary system is responsible for filtering the blood, excreting wastes, and helping to regulate electrolyte and water balance.
- The urinary system includes the kidneys, ureters, urinary bladder, and urethra; the bladder and urethra are the most common sites of infection.
- Common sites of infection in the male reproductive system include the urethra, as well as the testes, prostate and epididymis.
• The most common sites of infection in the female reproductive system are the vulva, vagina, cervix, and fallopian tubes.
• Infections of the urogenital tract can occur through colonization from the external environment, alterations in microbiota due to hormonal or other physiological and environmental changes, fecal contamination, and sexual transmission (STIs).

23.2 Bacterial Infections of the Urinary System
• Bacterial cystitis is commonly caused by fecal bacteria such as E. coli.
• Pyelonephritis is a serious kidney infection that is often caused by bacteria that travel from infections elsewhere in the urinary tract and may cause systemic complications.
• Leptospirosis is a bacterial infection of the kidney that can be transmitted by exposure to infected animal urine, especially in contaminated water. It is more common in tropical than in temperate climates.
• Nongonococcal urethritis (NGU) is commonly caused by C. trachomatis, M. genitalium, Ureaplasma urealyticum, and M. hominis.
• Diagnosis and treatment for bacterial urinary tract infections varies. Urinalysis (e.g., for leukocyte esterase levels, nitrite levels, microscopic evaluation, and culture of urine) is an important component in most cases. Broad-spectrum antibiotics are typically used.

23.3 Bacterial Infections of the Reproductive System
• Bacterial vaginosis is caused by an imbalance in the vaginal microbiota, with a decrease in lactobacilli and an increase in vaginal pH. G. vaginalis is the most common cause of bacterial vaginosis, which is associated with vaginal discharge, odor, burning, and itching.
• 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.
• Chlamydia is the most commonly reported STI and is caused by C. trachomatis. Most infections are asymptomatic, and infections that are not treated can spread to involve the epididymis of men and cause salpingitis and pelvic inflammatory disease in women.
• Syphilis is caused by T. pallidum and has three stages, primary, secondary, and tertiary. Primary syphilis is associated with a painless hard chancre lesion on genitalia. Secondary syphilis is associated with skin and mucous membrane lesions. Tertiary syphilis is the most serious and life-threatening, and can involve serious nervous system damage.
• Chancroid is an infection of the reproductive tract caused by H. ducreyi that results in the development of characteristic soft chancre.

23.4 Viral Infections of the Reproductive System
• Genital herpes is usually caused by HSV-2 (although HSV-1 can also be responsible) and may cause the development of infectious, potentially recurrent vesicles.
• Neonatal herpes can occur in babies born to infected mothers and can cause symptoms that range from relatively mild (more common) to severe.
• Human papillomaviruses are the most common sexually transmitted viruses and include strains that cause genital warts as well as strains that cause cervical cancer.

23.5 Fungal Infections of the Reproductive System
• Candida spp. are typically present in the normal microbiota in the body, including the skin, respiratory tract, gastrointestinal tract, and female urogenital system.
• Disruptions in the normal vaginal microbiota can lead to an overgrowth of Candida, causing vaginal candidiasis.
• Vaginal candidiasis can be treated with topical or oral fungicides. Prevention is difficult.
23.6 Protozoan Infections of the Urogenital System

- **Trichomoniasis** is a common STI caused by *Trichomonas vaginalis*.
- *T. vaginalis* is common at low levels in the normal microbiota.
- Trichomoniasis is often asymptomatic. When symptoms develop, trichomoniasis causes urinary discomfort, irritation, itching, burning, discharge from the penis (in men), and vaginal discharge (in women).
- Trichomoniasis is treated with the antiflagellate drugs tinidazole and metronidazole.

Review Questions

Multiple Choice

1. When it first leaves the kidney, urine flows through
   a. the urinary bladder.
   b. the urethra.
   c. the ureter.
   d. the glomeruli.

2. What part of the male urogenital tract is shared by the urinary and reproductive systems?
   a. the prostate gland
   b. the seminal vesicles
   c. the vas deferens
   d. the urethra

3. Which species is not associated with NGU?
   a. *Neisseria gonorrhoeae*
   b. *Mycoplasma hominis*
   c. *Chlamydia trachomatis*
   d. *Mycoplasma genitalium*

4. A strain of bacteria associated with a bladder infection shows gram-negative rods. What species is most likely to be the causative agent?
   a. *Mycoplasma hominis*
   b. *Escherichia coli*
   c. *Neisseria gonorrhoeae*
   d. *Chlamydia trachomatis*

5. Treponemal and non-treponemal serological testing can be used to test for
   a. vaginosis.
   b. chlamydia.
   c. syphilis.
   d. gonorrhea.

6. Lymphogranuloma venereum is caused by serovars of
   a. *Neisseria gonorrhoeae*.
   b. *Chlamydia trachomatis*.
   c. *Treponema pallidum*.
   d. *Haemophilus ducreyi*.

7. The latent stage of syphilis, which may last for years, can occur between
   a. the secondary and tertiary stages.
   b. the primary and secondary stages.
   c. initial infection and the primary stage.
   d. any of the three stages.

8. Based on its shape, which microbe is this?

9. Genital herpes is most commonly caused by
   a. herpes simplex virus 1.
   b. varicella-zoster virus.
   c. herpes simplex virus 2.
   d. cytomegalovirus.

10. Koilocytes are characteristic of
    a. cells infected with human papillomavirus
    b. cells infected with herpes simplex virus 2
    c. cells infected with all forms of herpesviruses
    d. cervical cancer cells
11. Which oral medication is recommended as an initial topical treatment for genital yeast infections?
   a. penicillin
   b. acyclovir
   c. fluconazole
   d. miconazole

12. What is the only common infection of the reproductive tract caused by a protozoan?
   a. gonorrhea
   b. chlamydia
   c. trichomoniasis
   d. candidiasis

13. Which test is preferred for detecting T. vaginalis because of its high sensitivity?
   a. NAAT
   b. wet mounts
   c. Pap tests
   d. all of the above are equally good

**Fill in the Blank**

14. The genus of bacteria found in the vagina that is important in maintaining a healthy environment, including an acidic pH, is _____.

15. Pyelonephritis is a potentially severe infection of the _____.

16. Soft chancres on the genitals are characteristic of the sexually transmitted disease known as _____.

17. Condylomata are _____.

18. The most common Candida species associated with yeast infections is _____.

19. Trichomoniasis is caused by _____.

**Short Answer**

20. When the microbial balance of the vagina is disrupted, leading to overgrowth of resident bacteria without necessarily causing inflammation, the condition is called _____.

21. Explain the difference between a sexually transmitted infection and a sexually transmitted disease.

22. In the figure shown here, where would cystitis occur?

23. What is pyuria?
24. Compare gonococcal and nongonococcal urethritis with respect to their symptoms and the pathogens that cause each disease.

25. Is it true that human papillomaviruses can always be detected by the presence of genital warts?

26. How is neonatal herpes transmitted?

27. Name three organisms (a bacterium, a fungus, and a protozoan) that are associated with vaginitis.

**Critical Thinking**

28. Epidemiological data show that the use of antibiotics is often followed by cases of vaginosis or vaginitis in women. Can you explain this finding?

29. What are some factors that would increase an individual’s risk of contracting leptospirosis?

30. Chlamydia is often asymptomatic. Why might it be important for an individual to know if he or she were infected?

31. 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?

32. Recently, studies have shown a reduction in the prevalence of some strains of HPV in younger women. What might be the reason for this?
Chapter 24

Digestive System Infections

Figure 24.1  *E. coli* O157:H7 causes serious foodborne illness. Curli fibers (adhesive surface fibers that are part of the extracellular matrix) help these bacteria adhere to surfaces and form biofilms. Pictured are two groups of cells, curli non-producing cells (left) and curli producing cells (right). (credit left, right: modification of work by USDA)

Chapter Outline

24.1 Anatomy and Normal Microbiota of the Digestive System
24.2 Microbial Diseases of the Mouth and Oral Cavity
24.3 Bacterial Infections of the Gastrointestinal Tract
24.4 Viral Infections of the Gastrointestinal Tract
24.5 Protozoan Infections of the Gastrointestinal Tract
24.6 Helminthic Infections of the Gastrointestinal Tract

Introduction

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.
## 24.1 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

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 24.2). 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.

### 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.

- What could have caused Carli’s signs and symptoms?

*Jump to the next Clinical Focus box.*
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 24.3). The salivary glands produce saliva, which lubricates food and contains digestive enzymes.
Figure 24.3  (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 24.4) 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 24.4  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.

**Check Your Understanding**

- 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 24.5).
The structure of the wall of the small intestine allows for the majority of nutrient absorption in the body. Villi are folds in the surface of the small intestine. Microvilli are cytoplasmic extensions on individual cells that increase the surface area for absorption. A light micrograph shows the shape of the villi. An electron micrograph shows the shape of the microvilli. 

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.

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 24.5), 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 24.6). 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 24.6](image)

**Figure 24.6** A magnified image of intestinal villi in the GI tract shows goblet cells. These cells are important in producing a protective layer of mucus.

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**Check Your Understanding**

- Compare and contrast the microbiota of the small and large intestines.

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**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**.

### Check Your Understanding

- List possible causes and signs and symptoms of food poisoning.

#### 24.2 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 biofilm called 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 24.7). 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 24.8). These substantial plaque biofilms can include a variety of bacterial species, including **Streptococcus** and **Actinomyces** species.
Figure 24.7  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 24.8  (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 24.8). 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.

Check Your Understanding

- Name some ways that microbes contribute to tooth decay.
- What is the most important cariogenic species of bacteria?

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 24.9). 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.\(^1\)[2][3] 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 24.9  Redness and irritation of the gums are evidence of gingivitis.

Over time, chronic gingivitis can develop into the more serious condition of periodontitis (Figure 24.10). 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 24.10  (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 24.11) 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 24.11 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)

![Image of inflamed gums](image.png)

**Check Your Understanding**

- How does gingivitis progress to periodontitis?

**Micro Connections**

**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 24.12). 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 24.12  (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 24.13)
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 24.13** 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 24.3). 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 24.14). 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 24.14  This child shows the characteristic parotid swelling associated with mumps. (credit: modification of work by Centers for Disease Control and Prevention)

Check Your Understanding

• Compare and contrast the signs and symptoms of herpetic gingivostomatitis, oral thrush, and mumps.

Disease Profile

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 24.15 summarizes the main characteristics of common oral infections.
<table>
<thead>
<tr>
<th>Disease</th>
<th>Pathogen</th>
<th>Signs and Symptoms</th>
<th>Transmission</th>
<th>Diagnostic Tests</th>
<th>Antimicrobial Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dental caries</td>
<td><em>Streptococcus mutans</em></td>
<td>Discoloration, softening, cavities in teeth</td>
<td>Non-transmissible; caused by bacteria of the normal oral microbiota</td>
<td>Visual examinations, X-rays</td>
<td>Oral antiseptics (e.g., Listerine)</td>
</tr>
<tr>
<td>Gingivitis and periodontitis</td>
<td><em>Porphyromonas, Streptococcus, Actinomyces</em></td>
<td>Inflammation and erosion of gums, bleeding, halitosis; erosion of cementum, leading</td>
<td>Non-transmissible; caused by bacteria of the normal oral microbiota</td>
<td>Visual examination, X-rays, measuring pockets in gums</td>
<td>Tetracycline, doxycycline, macrolides or beta-lactams. Mixture of antibiotics may be given.</td>
</tr>
<tr>
<td>Herpetic gingivostomatitis</td>
<td>Herpes simplex virus type 1 (HSV-1)</td>
<td>Lesions in mucous membranes of mouth</td>
<td>Contact with saliva or lesions of an infected person</td>
<td>Culture or biopsy</td>
<td>Acyclovir, famcyclovir, valacyclovir</td>
</tr>
<tr>
<td>Mumps</td>
<td>Mumps virus (a paramyxovirus)</td>
<td>Swelling of parotid glands, fever, headache, muscle pain, weakness, fatigue, loss of</td>
<td>Contact with saliva or respiratory droplets of an infected person</td>
<td>Virus culture or serologic tests for antibodies, enzyme immunoassay, RT-PCR</td>
<td>None for treatment; MMR vaccine for prevention</td>
</tr>
<tr>
<td>Oral thrush</td>
<td><em>Candida albicans, other Candida spp.</em></td>
<td>White patches and pseudomembranes in mouth, may cause bleeding</td>
<td>Non-transmissible; caused by overgrowth of <em>Candida</em> spp. in the normal oral microbiota; primarily affects infants and the immunocompromised</td>
<td>Microscopic analysis of oral samples</td>
<td>Clotrimazole, nystatin, fluconazole, or itraconazole; amphotericin B in severe cases</td>
</tr>
<tr>
<td>Trench mouth (acute necrotizing ulcerative gingivitis)</td>
<td><em>Prevotella intermedia, Fusobacterium species, Treponema vincentii, others</em></td>
<td>Erosion of gums, ulcers, substantial pain with chewing, halitosis</td>
<td>Non-transmissible; caused by members of the normal oral microbiota</td>
<td>Visual examinations, X-rays</td>
<td>Amoxicillin, amoxicillin clavulanate, clindamycin, or doxycycline</td>
</tr>
</tbody>
</table>

*Figure 24.15*
24.3 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 disease can 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 24.16).
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.

**Check Your Understanding**

- 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\(^4\) (Figure 24.17). Severe cases may require antibiotics such as ciprofloxacin and azithromycin, but these must be carefully prescribed because resistance is increasingly common.

![Figure 24.17](image)

**Figure 24.17** Red and white blood cells can be seen in this micrograph of a stool sample from a patient with shigellosis.

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**Check Your Understanding**

- Compare and contrast *Shigella* infections and intoxications.

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**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

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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 24.18). 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. 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.

![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)](https://www.cdc.gov/salmonella)

**Figure 24.18** 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.

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, 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 24.1 summarizes the characteristics of the four most common pathogenic groups.

<table>
<thead>
<tr>
<th>Group</th>
<th>Virulence Factors and Genes</th>
<th>Signs and Symptoms</th>
<th>Diagnostic Tests</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enterotoxigenic <em>E. coli</em> (ETEC)</td>
<td>Heat stable enterotoxin similar to cholera toxin</td>
<td>Relatively mild, watery diarrhea</td>
<td>Culturing, PCR</td>
<td>Self-limiting; if needed, fluoroquinolones, doxycycline, rifaximin, TMP/SMZ; antibiotic resistance is a problem</td>
</tr>
<tr>
<td>Enteroinvasive <em>E. coli</em> (EIEC)</td>
<td><em>inv</em> (invasive plasmid) genes</td>
<td>Relatively mild, watery diarrhea; dysentery or inflammatory colitis may occur</td>
<td>Culturing, PCR; testing for <em>inv</em> gene; additional assays to distinguish from <em>Shigella</em></td>
<td>Supportive therapy only; antibiotics not recommended</td>
</tr>
<tr>
<td>Enteropathogenic <em>E. coli</em> (EPEC)</td>
<td>Locus of enterocyte effacement (LEE) pathogenicity island</td>
<td>Severe fever, vomiting, nonbloody diarrhea, dehydration; potentially fatal</td>
<td>Culturing, PCR; detection of LEE lacking Shiga-like toxin genes</td>
<td>Self-limiting; if needed, fluoroquinolones, doxycycline, rifaximin (TMP/SMZ); antibiotic resistance is a problem</td>
</tr>
<tr>
<td>Enterohemorrhagic <em>E. coli</em> (EHEC)</td>
<td>Verotoxin</td>
<td>May be mild or very severe; bloody diarrhea; may result in HUS</td>
<td>Culturing; plate on MacConkey agar with sorbitol agar as it does not ferment sorbitol; PCR detection of LEE containing Shiga-like toxin genes</td>
<td>Antibiotics are not recommended due to the risk of HUS</td>
</tr>
</tbody>
</table>

Table 24.1
• 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.\(^7\)

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 24.19**).

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, ofloxacin, 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 24.19**)

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V. cholera is not the only Vibrio species that can cause disease. *V. parahaemolyticus* 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. parahaemolyticus* 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*.

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**Check Your Understanding**

- 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 24.20). 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.[8]

*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*. 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.

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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.[10][11]

**Check Your Understanding**

- 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 24.21). 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.


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.\(^{[12]}\)

**Check Your Understanding**

- 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.

**Check Your Understanding**

- Compare and contrast foodborne illnesses due to *B. cereus* and *Yersinia*.

Disease Profile

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 24.22 and Figure 24.23 the key features of common bacterial GI infections.
## Bacterial Infections of the GI Tract

<table>
<thead>
<tr>
<th>Disease</th>
<th>Pathogen</th>
<th>Signs and Symptoms</th>
<th>Transmission</th>
<th>Diagnostic Tests</th>
<th>Antimicrobial Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Bacillus cereus</em> infection</td>
<td><em>Bacillus cereus</em></td>
<td>Nausea, pain, abdominal cramps, diarrhea, or vomiting</td>
<td>Ingestion of contaminated rice or meat, even after cooking</td>
<td>Testing stool sample, vomitus, or uneaten food for presence of bacteria</td>
<td>None</td>
</tr>
<tr>
<td><em>Campylobacter jejuni</em> gastroenteritis</td>
<td><em>Campylobacter jejuni</em></td>
<td>Fever, diarrhea, cramps, vomiting, and sometimes dysentery; sometimes more severe organ or autoimmune effects</td>
<td>Ingestion of unpasteurized milk, undercooked chicken, or contaminated water</td>
<td>Culture on selective medium with elevated temperature and low oxygen concentration</td>
<td>Generally none; erythromycin or ciprofloxacin if necessary</td>
</tr>
<tr>
<td>Cholera</td>
<td><em>Vibrio cholerae</em></td>
<td>Severe diarrhea and fluid loss, potentially leading to shock, renal failure, and death</td>
<td>Ingestion of contaminated water or food</td>
<td>Culture on selective medium (TCBS agar); distinguished as oxidase positive with fermentative metabolisms</td>
<td>Generally none; tetracyclines, azithromycin, others if necessary</td>
</tr>
<tr>
<td><em>Clostridium difficile</em> infection</td>
<td><em>Clostridium difficile</em></td>
<td>Pseudomembranous colitis, watery diarrhea, fever, abdominal pain, loss of appetite, dehydration; in severe cases, perforation of the colon, sepsisemia, shock, and death</td>
<td>Overgrowth of <em>C. difficile</em> in the normal microbiota due to antibiotic use; hospital-acquired infections in immunocompromised patients</td>
<td>Detection of toxin in stool, nucleic acid amplification tests (e.g., PCR)</td>
<td>Discontinuation of previous antibiotic treatment; metronidazole or vancomycin</td>
</tr>
<tr>
<td><em>Clostridium perfringens</em> gastroenteritis (especially type A)</td>
<td><em>Clostridium perfringens</em></td>
<td>Mild cramps and diarrhea in most cases; in rare cases, hemorrhaging, vomiting, intestinal gangrene, and death</td>
<td>Ingestion of undercooked meats containing <em>C. perfringens</em> endospores</td>
<td>Detection of toxin or bacteria in stool or uneaten food</td>
<td>None</td>
</tr>
<tr>
<td><em>E. coli</em> infection</td>
<td>ETEC, EPEC, EIEC, EHEC</td>
<td>Watery diarrhea, dysentery, cramps, malaise, fever, chills, dehydration; in EHEC, possible severe complications such as hematolytic uremic syndrome</td>
<td>Ingestion of contaminated food or water</td>
<td>Tissue culture, immunochemical assays, PCR, gene probes</td>
<td>Not recommended for EIEC and EHEC, fluoroquinolones, doxycycline, rifaximin, and TMP/SMZ possible for ETEC and EPEC</td>
</tr>
</tbody>
</table>
## Bacterial Infections of the GI Tract (continued)

<table>
<thead>
<tr>
<th>Disease</th>
<th>Pathogen</th>
<th>Signs and Symptoms</th>
<th>Transmission</th>
<th>Diagnostic Tests</th>
<th>Antimicrobial Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peptic ulcers</td>
<td><em>Helicobacter pylori</em></td>
<td>Nausea, bloating, burping, lack of appetite, weight loss, perforation of stomach, blood in stools</td>
<td>Normal flora, can also be acquired via saliva; fecal-oral route via contaminated food and water</td>
<td>Breath test, detection of antibodies in blood, detection of bacteria in stool sample or stomach biopsy</td>
<td>Amoxicillin, clarithromycin, metronidazole, tetracycline, lansoprazole; antacids may also be given in combination with antibiotics</td>
</tr>
<tr>
<td>Salmonellosis</td>
<td><em>Salmonella enterica</em>, serotype Enteritides</td>
<td>Fever, nausea, vomiting, abdominal cramps, headache, diarrhea; can be fatal in infants</td>
<td>Ingestion of contaminated food, handling of eggshells or contaminated animals.</td>
<td>Culturing, serotyping and DNA fingerprinting</td>
<td>Not generally recommended; fluoroquinolones, ampicillin, others for immunocompromised patients</td>
</tr>
<tr>
<td>Shigellosis dysentery</td>
<td><em>Shigella dysenteriae</em>, <em>S. flexneri</em>, <em>S. boydii</em>, and <em>S. sonnei</em></td>
<td>Abdominal cramps, fever, diarrhea, dysentery; possible complications: reactive arthritis and hemolytic uremic syndrome</td>
<td>Fecal-oral route via contaminated food and water</td>
<td>Testing of stool samples for presence of blood and leukocytes; culturing, PCR, immunoassay for <em>S. dysenteriae</em></td>
<td>Ciprofloxacin, azithromycin</td>
</tr>
<tr>
<td>Staphylococcal food poisoning</td>
<td><em>Staphylococcus aureus</em></td>
<td>Rapid-onset nausea, diarrhea, vomiting lasting 24–48 hours; possible dehydration and change in blood pressure and heart rate</td>
<td>Ingestion of raw or undercooked meat or dairy products contaminated with staphylococcal enterotoxins</td>
<td>ELISA to detect enterotoxins in uneaten food, stool, or vomitus</td>
<td>None</td>
</tr>
<tr>
<td>Typhoid fever</td>
<td><em>S. enterica</em>, subtypes Typhi or Paratyphi</td>
<td>Aches, headaches, nausea, lethargy, diarrhea or constipation, possible rash; lethal perforation of intestine can occur</td>
<td>Fecal-oral route; may be spread by asymptomatic carriers</td>
<td>Culture of blood, stool, or bone marrow, serologic tests; PCR tests when available</td>
<td>Fluoroquinolones, ceftriaxone, azithromycin; preventive vaccine available</td>
</tr>
<tr>
<td>Yersinia infection</td>
<td><em>Yersinia enterocolitica</em>, <em>Y. pseudotuberculosis</em></td>
<td>Generally mild diarrhea and abdominal cramps; in some cases, bacteremia can occur, leading to severe complications</td>
<td>Fecal-oral route, typically via contaminated food or water</td>
<td>Testing stool samples, tissues, body fluids</td>
<td>Generally none; fluoroquinolones, aminoglycosides, others for systemic infections</td>
</tr>
</tbody>
</table>
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*.

- What should the doctor do now to treat Carli?

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

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**24.4 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.[13] Worldwide, diarrhea is the second leading cause of mortality for children under age five, and 70% of childhood gastroenteritis is viral.[14] 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 24.24).

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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.\textsuperscript{[15]} 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.\textsuperscript{[16]}

### 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.

Check Your Understanding

- Why are rotaviruses, noroviruses, and astroviruses more common in children?

Disease Profile

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.
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: hepatitis viruses A (HAV), B (HBV), C (HCV), D (HDV) and E (HEV) (Figure 24.26). 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.

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.

### Figure 24.26
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).
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 24.27). In severe cases, death from liver necrosis may occur.

![Healthy liver and inflamed liver](image)

**Figure 24.27** (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. 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.

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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 24.28). 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.
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. 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 24.28. 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

<table>
<thead>
<tr>
<th>Disease</th>
<th>Pathogen</th>
<th>Signs and Symptoms</th>
<th>Transmission</th>
<th>Antimicrobial Drugs</th>
<th>Vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis A</td>
<td>Hepatitisvirus A (HAV)</td>
<td>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</td>
<td>Contaminated food, water, objects, and person to person</td>
<td>None</td>
<td>Vaccine recommended for one year olds and high-risk adults</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Hepatitisvirus B (HBV)</td>
<td>Similar to Hepatitis A, but may progress to cirrhosis and liver failure; associated with liver cancer</td>
<td>Contact with infected body fluids (blood, semen, saliva), e.g., via IV drug use, sexual transmission, health-care workers treating infected patients</td>
<td>Interferon, entecavir, tenofovir, lamivudine, adefovir</td>
<td>Vaccine recommended for infants and high-risk adults</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>Hepatitisvirus C (HCV)</td>
<td>Often asymptomatic, with 75%–85% chronic carriers; may progress to cirrhosis and liver failure; associated with liver cancer</td>
<td>Contact with infected body fluids, e.g., via IV drug use, transfusions, sexual transmission</td>
<td>Depends on genotype and on whether cirrhosis is present; interferons, new treatment such as simeprevir plus sofosbuvir, ombitasvir/paritaprevir/ritonavir and dasabuvir</td>
<td>None available</td>
</tr>
<tr>
<td>Hepatitis D</td>
<td>Hepatitisvirus D (HDV)</td>
<td>Similar to hepatitis B; usually self-limiting within one to two weeks but can become chronic or fulminant in rare cases</td>
<td>Contact with infected blood; infections can only occur in patients already infected with hepatitis B</td>
<td>None</td>
<td>Hepatitis B vaccine protects against HDV</td>
</tr>
<tr>
<td>Hepatitis E</td>
<td>Hepatitisvirus E (HEV)</td>
<td>Generally asymptomatic or mild and self-limiting; typically does not cause chronic disease</td>
<td>Fecal-oral route, often in contaminated water or undercooked meat; most common in developing countries</td>
<td>Supportive treatment; usually self-limiting, but some strains can become chronic; antiviral and immunosuppressive possible for chronic cases</td>
<td>Vaccine available in China only</td>
</tr>
</tbody>
</table>

Figure 24.28
24.5 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 1.16). 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 trophozoite. 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 24.29) 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.

**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.\[^{19}\]

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 24.30).

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**Check Your Understanding**

- Which protozoan GI infections are common in the United States?

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**Disease Profile**

**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.

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24.6 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.[20] 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 24.32). 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.

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**Figure 24.32**  (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)

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**Check Your Understanding**

- Describe the route by which *A. lumbricoides* reaches the host’s intestines as an adult worm.

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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 duodenale*, 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 24.33).

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.

![Figure 24.33](Figure 24.33) (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)

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.

Check Your Understanding

- 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. 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 24.34*).

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.

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Figure 24.34  (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 24.35). 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.

Figure 24.35  (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 24.36).

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 24.36](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)

Check Your Understanding

- 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 24.37). Figure 5.23 illustrates the life cycle of a tapeworm.

![Figure 24.37](image)

(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.\textsuperscript{[22]}

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.\textsuperscript{[23]}

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, \textit{Echinococcus granulosus}, causes a serious infection known as \textbf{hydatid disease (cystic echinococcosis)}. \textit{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, \textit{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.

\textit{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 (albendazole or mebendazole).

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Check Your Understanding

- 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 24.38).

\begin{itemize}
\end{itemize}
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. Clonorchiasis 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 5.22).

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.
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.
<table>
<thead>
<tr>
<th>Disease</th>
<th>Causative Agent(s)</th>
<th>Mode of Transmission</th>
<th>Laboratory Tests</th>
<th>Symptoms</th>
<th>Treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascariasis</td>
<td>Ascaris lumbricoides</td>
<td>Eggs in faecally contaminated food or water</td>
<td>Microscopic examination of the stool, imaging</td>
<td>Shortness of breath, cough, nausea, diarrhea, blood in stool, abdominal pain, weight loss, fatigue</td>
<td>Self-limiting within 1 to 2 years; albendazole and mebendazole if needed</td>
</tr>
<tr>
<td>Hookworm</td>
<td>Necator americanus, Ancylostoma duodenale</td>
<td>Larvae in soil contaminated by dog or cat feces penetrate skin</td>
<td>Microscopic examination of stool (may require a concentration procedure)</td>
<td>Cough, irchy rash, loss of appetite, abdominal pain, diarrhea; in children, may affect physical and cognitive growth</td>
<td>Albendazole and mebendazole; pyrantel pamoatamay if needed</td>
</tr>
<tr>
<td>Strongyloidiasis</td>
<td>Strongyloides stercoralis</td>
<td>Soil-dwelling larvae penetrate the skin, usually bare feet</td>
<td>Microscopic examination of stool over several days (daily at least 7); some serologic testing available</td>
<td>Often asymptomatic; cough (sometimes bloody), skin rash, abdominal pain, and diarrhea; in immunosuppressed patients, may become disseminated, causing serious and potentially fatal complications</td>
<td>Ivermectin (preferred), albendazole</td>
</tr>
<tr>
<td>Enterobiasis (pinworm)</td>
<td>Enterobias vermicularis</td>
<td>Fecal–oral route</td>
<td>Observation of eggs or worms from anal area; examination of samples under fingernails</td>
<td>Itching around the anus, abdominal pain, insomnia, irritation of female genital tract</td>
<td>Mebendazole, albendazole, pyrantel pamoate</td>
</tr>
<tr>
<td>Trichuriasis (whipworm)</td>
<td>Trichuris trichiura</td>
<td>Fecal contamination or fertilization in soil</td>
<td>Microscopic examination of stool</td>
<td>Abdominal pain, anemia, diarrhea that may be bloody</td>
<td>Albendazole, mebendazole, ivermectin if needed</td>
</tr>
<tr>
<td>Trichinosis</td>
<td>Trichinella spiralis</td>
<td>Eating raw or undercooked pork or other meat of infected animal</td>
<td>Clinical history, muscle biopsy, serological testing, enzyme immunoassay</td>
<td>Diarrhea, constipation, abdominal pain, headache, cough, chills, light sensitivity, muscle pain, fever, conjunctivitis; in severe cases may affect motor coordination, breathing, heart function</td>
<td>Albendazole, mebendazole if needed</td>
</tr>
<tr>
<td>Taeniasis and cysticercosis</td>
<td>Taenia solium, T. saginata, T. asiatica, Diphyllobothrium latum</td>
<td>Eating raw or undercooked beef or pork from infected animal</td>
<td>Observation of worm segments or microscopic eggs in stool samples</td>
<td>Asymptomatic or mild GI distress; cysts in muscle, eye, or brain (cysticercosis); brain cysts can cause headaches, seizures, or death</td>
<td>Praziquantel or niclosamide</td>
</tr>
<tr>
<td>Cystic echinococcosis</td>
<td>Echinococcus granulosus (cystic)</td>
<td>Exposure to eggs in feces of infected dogs or livestock</td>
<td>Imaging; serological testing including ELISA and indirect hemagglutinin test</td>
<td>Cysts in lungs, liver, and other organs causing nausea, GI distress, and weight loss; severe anaphylaxis or death if cysts burst</td>
<td>Surgical removal or aspiration of cysts or chemotherapy with albendazole or mebendazole</td>
</tr>
<tr>
<td>Liver fluke infections</td>
<td>Fasciola hepatica, F. gigantica, C. sinensis, Opisthorchis viverrini, O. felineus</td>
<td>Eating raw or undercooked aquatic plants (Fasciola spp.) or freshwater fish (Clonorchis spp.) contaminated with eggs or cysts</td>
<td>Microscopic examination of eggs in stool or other specimens; immunoassays</td>
<td>Fever, malaise, anemia, abdominal symptoms, transaminitis; cholargitis, cirrhosis, pancreaticitis, cholecystitis, gall stones in chronic phase</td>
<td>Triclabendazole (preferred) for Fasciola spp.; praziquantel and albendazole for C. sinensis and Opisthorchis spp.</td>
</tr>
<tr>
<td>Fascioliasis (intestinal fluke)</td>
<td>Fasciola buskii</td>
<td>Eating raw or undercooked aquatic plants containing cysts</td>
<td>Microscopic examination of eggs in stool or other samples; immunoassays</td>
<td>Diarrhea, abdominal pain; in severe cases, vomiting, nausea, intestinal obstruction, anemia, allergic reactions</td>
<td>Praziquantel</td>
</tr>
</tbody>
</table>

Figure 24.39
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 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.

Go back to the previous Clinical Focus box.

### Summary

#### 24.1 Anatomy and Normal Microbiota of the Digestive System
- 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.

#### 24.2 Microbial Diseases of the Mouth and Oral Cavity
- 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.

#### 24.3 Bacterial Infections of the Gastrointestinal Tract
- 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.

### 24.4 Viral Infections of the Gastrointestinal Tract
- 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.

### 24.5 Protozoan Infections of the Gastrointestinal Tract
- *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.

### 24.6 Helminthic Infections of the Gastrointestinal Tract
- 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 *ascarisis*.
- *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 *enterobiosis*.
- *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.

### 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.

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

3. What pathogen is the most important contributor to biofilms in plaque?
   a. Staphylococcus aureus
   b. Streptococcus mutans
   c. Escherichia coli
   d. Clostridium difficile

4. What type of organism causes thrush?
   a. a bacterium
   b. a virus
   c. a fungus
   d. a protozoan

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

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.

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

8. Which species of Shigella has a type that produces Shiga toxin?
   a. S. boydii
   b. S. flexneri
   c. S. dysenteriae
   d. S. sonnei

9. Which type of bacterium produces an A-B toxin?
   a. Salmonella
   b. Vibrio cholera
   c. ETEC
   d. Shigella dysenteriae

10. Which form of hepatitis virus can only infect an individual who is already infected with another hepatitis virus?
    a. HDV
    b. HAV
    c. HBV
    d. HEV

11. Which cause of viral gastroenteritis commonly causes projectile vomiting?
    a. hepatitis virus
    b. Astroviruses
    c. Rotavirus
    d. Noroviruses

12. Which protozoan is associated with the ability to cause severe dysentery?
    a. Giardia lamblia
    b. Cryptosporidium hominis
    c. Cyclospora cayetanesis
    d. Entamoeba histolytica

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
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?

![Figure 24.41](credit: Dr. Stan Erlandsen, Centers for Disease Control and Prevention)

- a. *Giardia lamblia*
- b. *Cryptosporidium hominis*
- c. *Cyclospora cayetanensis*
- d. *Entamoeba histolytica*

15. What is another name for *Trichuris trichiura*?
- a. pinworm
- b. whipworm
- c. hookworm
- d. ascariasis

16. Which type of helminth infection can be diagnosed using tape?
- a. pinworm
- b. whipworm
- c. hookworm
- d. tapeworm

**Fill in the Blank**

17. The part of the gastrointestinal tract with the largest natural microbiota is the _________.

18. When plaque becomes heavy and hardened, it is called dental calculus or _________.

19. Antibiotic associated pseudomembranous colitis is caused by _________.

20. Jaundice results from a buildup of _________.

21. Chronic _________ infections cause the unique sign of disease of greasy stool and are often resistant to treatment.

22. Liver flukes are often found in the _________ duct.

**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 make 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.
Chapter 25

Circulatory and Lymphatic System Infections

Figure 25.1  Yellow fever is a viral hemorrhagic disease that can cause liver damage, resulting in jaundice (left) as well as serious and sometimes fatal complications. The virus that causes yellow fever is transmitted through the bite of a biological vector, the Aedes aegypti mosquito (right). (credit left: modification of work by Centers for Disease Control and Prevention; credit right: modification of work by James Gathany, Centers for Disease Control and Prevention)

Chapter Outline

25.1 Anatomy of the Circulatory and Lymphatic Systems
25.2 Bacterial Infections of the Circulatory and Lymphatic Systems
25.3 Viral Infections of the Circulatory and Lymphatic Systems
25.4 Parasitic Infections of the Circulatory and Lymphatic Systems

Introduction

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. 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. 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.

25.1 Anatomy of the Circulatory and Lymphatic Systems

Learning Objectives

- Describe the major anatomical features of the circulatory and lymphatic systems
- Explain why the circulatory and lymphatic systems lack normal microbiota
- Explain how microorganisms overcome defenses of the circulatory and lymphatic systems to cause infection
- Describe general signs and symptoms of disease associated with infections of the circulatory and lymphatic systems

The circulatory and lymphatic systems are networks of vessels and a pump that transport blood and lymph, respectively, throughout the body. When these systems are infected with a microorganism, the network of vessels can facilitate the rapid dissemination of the microorganism to other regions of the body, sometimes with serious results.

In this section, we will examine some of the key anatomical features of the circulatory and lymphatic systems, as well as general signs and symptoms of infection.

The Circulatory System

The circulatory (or cardiovascular) system is a closed network of organs and vessels that moves blood around the body (Figure 25.2). The primary purposes of the circulatory system are to deliver nutrients, immune factors, and oxygen to tissues and to carry away waste products for elimination. The heart is a four-chambered pump that propels the blood throughout the body. Deoxygenated blood enters the right atrium through the superior vena cava and the inferior vena cava after returning from the body. The blood next passes through the tricuspid valve to enter the right ventricle. When the heart contracts, the blood from the right ventricle is pumped through the pulmonary arteries to the lungs. There, the blood is oxygenated at the alveoli and returns to the heart through the pulmonary veins. The oxygenated blood is received at the left atrium and proceeds through the mitral valve to the left ventricle. When the heart contracts, the oxygenated blood is pumped throughout the body via a series of thick-walled vessels called arteries. The first and largest artery is called the aorta. The arteries sequentially branch and decrease in size (and are called arterioles) until they end in a network of smaller vessels called capillaries. The capillary beds are located in the interstitial spaces within tissues and release nutrients, immune factors, and oxygen to those tissues. The capillaries connect to a series of vessels called venules, which increase in size to form the veins. The veins join together into

Clinical Focus

Part 1

Barbara is a 43-year-old patient who has been diagnosed with metastatic inflammatory breast cancer. To facilitate her ongoing chemotherapy, her physician implanted a port attached to a central venous catheter. At a recent checkup, she reported feeling restless and complained that the site of the catheter had become uncomfortable. After removing the dressing, the physician observed that the surgical site appeared red and was warm to the touch, suggesting a localized infection. Barbara's was also running a fever of 38.2 °C (100.8 °F). Her physician treated the affected area with a topical antiseptic and applied a fresh dressing. She also prescribed a course of the antibiotic oxacillin.

- Based on this information, what factors likely contributed to Barbara’s condition?
- What is the most likely source of the microbes involved?

Jump to the next Clinical Focus box.
larger vessels as they transfer blood back to the heart. The largest veins, the superior and inferior vena cava, return the blood to the right atrium.

**Figure 25.2** The major components of the human circulatory system include the heart, arteries, veins, and capillaries. This network delivers blood to the body’s organs and tissues. (credit top left: modification of work by Mariana Ruiz Villareal; credit bottom right: modification of work by Bruce Blaus)

Other organs play important roles in the circulatory system as well. The kidneys filter the blood, removing waste products and eliminating them in the urine. The liver also filters the blood and removes damaged or defective red blood cells. The spleen filters and stores blood, removes damaged red blood cells, and is a reservoir for immune factors. All of these filtering structures serve as sites for entrapment of microorganisms and help maintain an environment free of microorganisms in the blood.

**The Lymphatic System**

The lymphatic system is also a network of vessels that run throughout the body (Figure 25.3). However, these vessels do not form a full circulating system and are not pressurized by the heart. Rather, the lymphatic system is
an open system with the fluid moving in one direction from the extremities toward two drainage points into veins just above the heart. Lymphatic fluids move more slowly than blood because they are not pressurized. Small lymph capillaries interact with blood capillaries in the interstitial spaces in tissues. Fluids from the tissues enter the lymph capillaries and are drained away (Figure 25.4). These fluids, termed lymph, also contain large numbers of white blood cells.
The lymphatic system contains two types of lymphoid tissues. The **primary lymphoid tissue** includes bone marrow and the thymus. Bone marrow contains the hematopoietic stem cells (HSC) that differentiate and mature into the various types of blood cells and lymphocytes (see **Figure 17.12**). The **secondary lymphoid tissues** include the spleen, lymph nodes, and several areas of diffuse lymphoid tissues underlying epithelial membranes. The **spleen**, an encapsulated structure, filters blood and captures pathogens and antigens that pass into it (**Figure 25.5**). The spleen contains specialized macrophages and dendritic cells that are crucial for antigen presentation, a mechanism critical for activation of T lymphocytes and B lymphocytes (see **Major Histocompatibility Complexes and Antigen-Presenting Cells**). Lymph nodes are bean-shaped organs situated throughout the body. These structures contain areas called germinal centers that are rich in B and T lymphocytes. The **lymph nodes** also contain macrophages and dendritic cells for antigen presentation. Lymph from nearby tissues enters the lymph node through afferent lymphatic vessels and encounters these lymphocytes as it passes through; the lymph exits the lymph node through the efferent lymphatic vessels (**Figure 25.5**).
Figure 25.5  (a) The spleen is a lymphatic organ located in the upper left quadrant of the abdomen near the stomach and left kidney. It contains numerous phagocytes and lymphocytes that combat and prevent circulatory infections by killing and removing pathogens from the blood. (b) Lymph nodes are masses of lymphatic tissue located along the larger lymph vessels. They contain numerous lymphocytes that kill and remove pathogens from lymphatic fluid that drains from surrounding tissues.

Link to Learning

The lymphatic system filters fluids that have accumulated in tissues before they are returned to the blood. A brief overview of this process is provided at this (https://openstax.org/l/22lymphatic) website.

Check Your Understanding

- What is the main function of the lymphatic system?

Infections of the Circulatory System

Under normal circumstances, the circulatory system and the blood should be sterile; the circulatory system has no normal microbiota. Because the system is closed, there are no easy portals of entry into the circulatory system for microbes. Those that are able to breach the body’s physical barriers and enter the bloodstream encounter a host of circulating immune defenses, such as antibodies, complement proteins, phagocytes, and other immune cells. Microbes often gain access to the circulatory system through a break in the skin (e.g., wounds, needles, intravenous catheters, insect bites) or spread to the circulatory system from infections in other body sites. For example, microorganisms causing pneumonia or renal infection may enter the local circulation of the lung or kidney and spread from there throughout the circulatory network.

If microbes in the bloodstream are not quickly eliminated, they can spread rapidly throughout the body, leading to serious, even life-threatening infections. Various terms are used to describe conditions involving microbes in the
The term **bacteremia** refers to bacteria in the blood. If bacteria are reproducing in the blood as they spread, this condition is called **septicemia**. The presence of viruses in the blood is called **viremia**. Microbial toxins can also be spread through the circulatory system, causing a condition termed **toxemia**.

Microbes and microbial toxins in the blood can trigger an inflammatory response so severe that the inflammation damages host tissues and organs more than the infection itself. This counterproductive immune response is called **systemic inflammatory response syndrome (SIRS)**, and it can lead to the life-threatening condition known as **sepsis**. Sepsis is characterized by the production of excess cytokines that leads to classic signs of inflammation such as fever, vasodilation, and edema (see **Inflammation and Fever**). In a patient with sepsis, the inflammatory response becomes dysregulated and disproportionate to the threat of infection. Critical organs such as the heart, lungs, liver, and kidneys become dysfunctional, resulting in increased heart and respiratory rates, and disorientation. If not treated promptly and effectively, patients with sepsis can go into shock and die.

Certain infections can cause inflammation in the heart and blood vessels. Inflammation of the endocardium, the inner lining of the heart, is called **endocarditis** and can result in damage to the heart valves severe enough to require surgical replacement. Inflammation of the pericardium, the sac surrounding the heart, is called **pericarditis**. The term **myocarditis** refers to the inflammation of the heart’s muscle tissue. Pericarditis and myocarditis can cause fluid to accumulate around the heart, resulting in congestive heart failure. Inflammation of blood vessels is called **vasculitis**. Although somewhat rare, vasculitis can cause blood vessels to become damaged and rupture; as blood is released, small red or purple spots called **petechiae** appear on the skin. If the damage of tissues or blood vessels is severe, it can result in reduced blood flow to the surrounding tissues. This condition is called **ischemia**, and it can be very serious. In severe cases, the affected tissues can die and become necrotic; these situations may require surgical debridement or amputation.

**Check Your Understanding**

- Why does the circulatory system have no normal microbiota?
- Explain why the presence of microbes in the circulatory system can lead to serious consequences.

**Infections of the Lymphatic System**

Like the circulatory system, the lymphatic system does not have a normal microbiota, and the large numbers of immune cells typically eliminate transient microbes before they can establish an infection. Only microbes with an array of virulence factors are able to overcome these defenses and establish infection in the lymphatic system. However, when a localized infection begins to spread, the lymphatic system is often the first place the invading microbes can be detected.

Infections in the lymphatic system also trigger an inflammatory response. Inflammation of lymphatic vessels, called **lymphangitis**, can produce visible red streaks under the skin. Inflammation in the lymph nodes can cause them to swell. A swollen lymph node is referred to as a **bubo**, and the condition is referred to as **lymphadenitis**.

**25.2 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. 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**).

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. 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.

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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,[6] 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.

**Check Your Understanding**

- 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

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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 nongonococcal infectious arthritis will suffer permanent joint damage and mortality rates range from 5% to 20%.[7] Mortality rates are higher among the elderly.[8]

**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.[9]

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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.

Check Your Understanding

- What bacterium the most common cause of both septic arthritis and osteomyelitis?

Rheumatic Fever

Infections with *S. pyogenes* have a variety of manifestations and complications generally called sequelae. As mentioned, the bacterium can cause supplicative infections like puerperal fever. However, this microbe can also cause nonsuppurative sequelae in the form of acute rheumatic fever (ARF), which can lead to rheumatic heart disease, thus impacting the circulatory system. Rheumatic fever occurs primarily in children a minimum of 2–3 weeks after an episode of untreated or inadequately treated pharyngitis (see Bacterial Infections of the Respiratory Tract). At one time, rheumatic fever was a major killer of children in the US; today, however, it is rare in the US because of early diagnosis and treatment of streptococcal pharyngitis with antibiotics. In parts of the world where diagnosis and treatment are not readily available, acute rheumatic fever and rheumatic heart disease are still major causes of mortality in children.¹⁰

Rheumatic fever is characterized by a variety of diagnostic signs and symptoms caused by nonsuppurative, immune-mediated damage resulting from a cross-reaction between patient antibodies to bacterial surface proteins and similar proteins found on cardiac, neuronal, and synovial tissues. Damage to the nervous tissue or joints, which leads to joint pain and swelling, is reversible. However, damage to heart valves can be irreversible and is worsened by repeated episodes of acute rheumatic fever, particularly during the first 3–5 years after the first rheumatic fever attack. The inflammation of the heart valves caused by cross-reacting antibodies leads to scarring and stiffness of the valve leaflets. This, in turn, produces a characteristic heart murmur. Patients who have previously developed rheumatic fever and who subsequently develop recurrent pharyngitis due to *S. pyogenes* are at high risk for a recurrent attacks of rheumatic fever.

The American Heart Association recommends¹¹ a treatment regimen consisting of benzathine benzylpenicillin every 3 or 4 weeks, depending on the patient’s risk for reinfection. Additional prophylactic antibiotic treatment may be recommended depending on the age of the patient and risk for reinfection.

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Bacterial Endocarditis and Pericarditis

The endocardium is a tissue layer that lines the muscles and valves of the heart. This tissue can become infected by a variety of bacteria, including gram-positive cocci such as *Staphylococcus aureus*, viridans streptococci, and *Enterococcus faecalis*, and the gram-negative so-called HACEK bacilli: *Haemophilus* spp., *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella kingae*. The resulting inflammation is called endocarditis, which can be described as either acute or subacute. Causative agents typically enter the bloodstream during accidental or intentional breaches in the normal barrier defenses (e.g., dental procedures, body piercings, catheterization, wounds). Individuals with preexisting heart damage, prosthetic valves and other cardiac devices, and those with a history of rheumatic fever have a higher risk for endocarditis. This disease can rapidly destroy the heart valves and, if untreated, lead to death in just a few days.

In **subacute bacterial endocarditis**, heart valve damage occurs slowly over a period of months. During this time, blood clots form in the heart, and these protect the bacteria from phagocytes. These patches of tissue-associated bacteria are called vegetations. The resulting damage to the heart, in part resulting from the immune response causing fibrosis of heart valves, can necessitate heart valve replacement (Figure 25.6). Outward signs of subacute endocarditis may include a fever.

Diagnosis of infective endocarditis is determined using the combination of blood cultures, echocardiogram, and clinical symptoms. In both acute and subacute endocarditis, treatment typically involves relatively high doses of intravenous antibiotics as determined by antimicrobial susceptibility testing. Acute endocarditis is often treated with a combination of ampicillin, nafcillin, and gentamicin for synergistic coverage of *Staphylococcus* spp. and *Streptococcus* spp. Prosthetic-valve endocarditis is often treated with a combination of vancomycin, rifampin, and gentamicin. Rifampin is necessary to treat individuals with infection of prosthetic valves or other foreign bodies because rifampin can penetrate the biofilm of most of the pathogens that infect these devices.

*Staphylococcus* spp. and *Streptococcus* spp. can also infect and cause inflammation in the tissues surrounding the heart, a condition called acute pericarditis. Pericarditis is marked by chest pain, difficulty breathing, and a dry cough. In most cases, pericarditis is self-limiting and clinical intervention is not necessary. Diagnosis is made with the aid of a chest radiograph, electrocardiogram, echocardiogram, aspirate of pericardial fluid, or biopsy of pericardium. Antibacterial medications may be prescribed for infections associated with pericarditis; however, pericarditis can also be caused by other pathogens, including viruses (e.g., echovirus, influenza virus), fungi (e.g., *Histoplasma* spp., *Coccidioides* spp.), and eukaryotic parasites (e.g., *Toxoplasma* spp.).

![bacterial vegetations](image)

**Figure 25.6** The heart of an individual who had subacute bacterial endocarditis of the mitral valve. Bacterial vegetations are visible on the valve tissues. (credit: modification of work by Centers for Disease Control and Prevention)
Gas Gangrene

Traumatic injuries or certain medical conditions, such as diabetes, can cause damage to blood vessels that interrupts blood flow to a region of the body. When blood flow is interrupted, tissues begin to die, creating an anaerobic environment in which anaerobic bacteria can thrive. This condition is called ischemia. Endospores of the anaerobic bacterium *Clostridium perfringens* (along with a number of other *Clostridium* spp. from the gut) can readily germinate in ischemic tissues and colonize the anaerobic tissues.

The resulting infection, called gas gangrene, is characterized by rapidly spreading myonecrosis (death of muscle tissue). The patient experiences a sudden onset of excruciating pain at the infection site and the rapid development of a foul-smelling wound containing gas bubbles and a thin, yellowish discharge tinged with a small amount of blood. As the infection progresses, edema and cutaneous blisters containing bluish-purple fluid form. The infected tissue becomes liquefied and begins sloughing off. The margin between necrotic and healthy tissue often advances several inches per hour even with antibiotic therapy. Septic shock and organ failure frequently accompany gas gangrene; when patients develop sepsis, the mortality rate is greater than 50%.

α-Toxin and theta (θ) toxin are the major virulence factors of *C. perfringens* implicated in gas gangrene. α-Toxin is a lipase responsible for breaking down cell membranes; it also causes the formation of thrombi (blood clots) in blood vessels, contributing to the spread of ischemia. θ-Toxin forms pores in the patient’s cell membranes, causing cell lysis. The gas associated with gas gangrene is produced by *Clostridium*’s fermentation of butyric acid, which produces hydrogen and carbon dioxide that are released as the bacteria multiply, forming pockets of gas in tissues (Figure 25.7).

Gas gangrene is initially diagnosed based on the presence of the clinical signs and symptoms described earlier in this section. Diagnosis can be confirmed through Gram stain and anaerobic cultivation of wound exudate (drainage) and tissue samples on blood agar. Treatment typically involves surgical debridement of any necrotic tissue; advanced cases may require amputation. Surgeons may also use vacuum-assisted closure (VAC), a surgical technique in which vacuum-assisted drainage is used to remove blood or serous fluid from a wound or surgical site to speed recovery. The most common antibiotic treatments include penicillin G and clindamycin. Some cases are also treated with hyperbaric oxygen therapy because *Clostridium* spp. are incapable of surviving in oxygen-rich environments.

![Figure 25.7](image-url) (a) In this image of a patient with gas gangrene, note the bluish-purple discoloration around the bicep and the irregular margin of the discolored tissue indicating the spread of infection. (b) A radiograph of the arm shows a darkening in the tissue, which indicates the presence of gas. (credit a, b: modification of work by Aggelidakis J, Lasithiotakis K, Topalidou A, Koutroumpas J, Kouvidis G, and Katonis P)
Tularemia

Infection with the gram-negative bacterium *Francisella tularensis* causes tularemia (or rabbit fever), a zoonotic infection in humans. *F. tularensis* is a facultative intracellular parasite that primarily causes illness in rabbits, although a wide variety of domesticated animals are also susceptible to infection. Humans can be infected through ingestion of contaminated meat or, more typically, handling of infected animal tissues (e.g., skinning an infected rabbit). Tularemia can also be transmitted by the bites of infected arthropods, including the dog tick (*Dermacentor variabilis*), the lone star tick (*Amblyomma americanum*), the wood tick (*Dermacentor andersoni*), and deer flies (*Chrysops* spp.). Although the disease is not directly communicable between humans, exposure to aerosols of *F. tularensis* can result in life-threatening infections. *F. tularensis* is highly contagious, with an infectious dose of as few as 10 bacterial cells. In addition, pulmonary infections have a 30%–60% fatality rate if untreated. For these reasons, *F. tularensis* is currently classified and must be handled as a biosafety level-3 (BSL-3) organism and as a potential biological warfare agent.

Following introduction through a break in the skin, the bacteria initially move to the lymph nodes, where they are ingested by phagocytes. After escaping from the phagosome, the bacteria grow and multiply intracellularly in the cytoplasm of phagocytes. They can later become disseminated through the blood to other organs such as the liver, lungs, and spleen, where they produce masses of tissue called granulomas (Figure 25.8). After an incubation period of about 3 days, skin lesions develop at the site of infection. Other signs and symptoms include fever, chills, headache, and swollen and painful lymph nodes.

**Figure 25.8** (a) A skin lesion appears at the site of infection on the hand of an individual infected with *Francisella tularensis*. (b) A scanning electron micrograph shows the coccobacilli cells (blue) of *F. tularensis*. (credit a: modification of work by Centers for Disease Control and Prevention; credit b: modification of work by NIAID)

A direct diagnosis of tularemia is challenging because it is so contagious. Once a presumptive diagnosis of tularemia is made, special handling is required to collect and process patients’ specimens to prevent the infection of healthcare workers. Specimens suspected of containing *F. tularensis* can only be handled by BSL-2 or BSL-3 laboratories registered with the Federal Select Agent Program, and individuals handling the specimen must wear protective equipment and use a class II biological safety cabinet.

Tularemia is relatively rare in the US, and its signs and symptoms are similar to a variety of other infections that may need to be ruled out before a diagnosis can be made. Direct fluorescent-antibody (DFA) microscopic examination using antibodies specific for *F. tularensis* can rapidly confirm the presence of this pathogen. Culturing this microbe is difficult because of its requirement for the amino acid cysteine, which must be supplied as an extra nutrient in culturing media. Serological tests are available to detect an immune response against the bacterial pathogen. In patients with suspected infection, acute- and convalescent-phase serum samples are required to confirm an active

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infection. PCR-based tests can also be used for clinical identification of direct specimens from body fluids or tissues as well as cultured specimens. In most cases, diagnosis is based on clinical findings and likely incidents of exposure to the bacterium. The antibiotics streptomycin, gentamycin, doxycycline, and ciprofloxacin are effective in treating tularemia.

**Brucellosis**

Species in the genus *Brucella* are gram-negative facultative intracellular pathogens that appear as coccobacilli. Several species cause zoonotic infections in animals and humans, four of which have significant human pathogenicity: *B. abortus* from cattle and buffalo, *B. canis* from dogs, *B. suis* from swine, and *B. melitensis* from goats, sheep, and camels. Infections by these pathogens are called brucellosis, also known as undulant fever, “Mediterranean fever,” or “Malta fever.” Vaccination of animals has made brucellosis a rare disease in the US, but it is still common in the Mediterranean, south and central Asia, Central and South America, and the Caribbean. Human infections are primarily associated with the ingestion of meat or unpasteurized dairy products from infected animals. Infection can also occur through inhalation of bacteria in aerosols when handling animal products, or through direct contact with skin wounds. In the US, most cases of brucellosis are found in individuals with extensive exposure to potentially infected animals (e.g., slaughterhouse workers, veterinarians).

Two important virulence factors produced by *Brucella* spp. are urease, which allows ingested bacteria to avoid destruction by stomach acid, and lipopolysaccharide (LPS), which allows the bacteria to survive within phagocytes. After gaining entry to tissues, the bacteria are phagocytized by host neutrophils and macrophages. The bacteria then escape from the phagosome and grow within the cytoplasm of the cell. Bacteria phagocytized by macrophages are disseminated throughout the body. This results in the formation of granulomas within many body sites, including bone, liver, spleen, lung, genitourinary tract, brain, heart, eye, and skin. Acute infections can result in undulant (relapsing) fever, but untreated infections develop into chronic disease that usually manifests as acute febrile illness (fever of 40–41 °C [104–105.8 °F]) with recurring flu-like signs and symptoms.

*Brucella* is only reliably found in the blood during the acute fever stage; it is difficult to diagnose by cultivation. In addition, *Brucella* is considered a BSL-3 pathogen and is hazardous to handle in the clinical laboratory without protective clothing and at least a class II biological safety cabinet. Agglutination tests are most often used for serodiagnosis. In addition, enzyme-linked immunosorbent assays (ELISAs) are available to determine exposure to the organism. The antibiotics doxycycline or ciprofloxacin are typically prescribed in combination with rifampin; gentamicin, streptomycin, and trimethoprim-sulfamethoxazole (TMP-SMZ) are also effective against *Brucella* infections and can be used if needed.

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### Check Your Understanding

- Compare the pathogenesis of tularemia and brucellosis.

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**Cat-Scratch Disease**

The zoonosis **cat-scratch disease (CSD)** (or cat-scratch fever) is a bacterial infection that can be introduced to the lymph nodes when a human is bitten or scratched by a cat. It is caused by the facultative intracellular gram-negative bacterium *Bartonella henselae*. Cats can become infected from flea feces containing *B. henselae* that they ingest while grooming. Humans become infected when flea feces or cat saliva (from claws or licking) containing *B. henselae* are introduced at the site of a bite or scratch. Once introduced into a wound, *B. henselae* infects red blood cells.

*B. henselae* invasion of red blood cells is facilitated by adhesins associated with outer membrane proteins and a secretion system that mediates transport of virulence factors into the host cell. Evidence of infection is indicated if a small nodule with pus forms in the location of the scratch 1 to 3 weeks after the initial injury. The bacteria then migrate to the nearest lymph nodes, where they cause swelling and pain. Signs and symptoms may also include fever, chills, and fatigue. Most infections are mild and tend to be self-limiting. However, immunocompromised patients may
develop bacillary angiomatosis (BA), characterized by the proliferation of blood vessels, resulting in the formation of tumor-like masses in the skin and internal organs; or bacillary peliosis (BP), characterized by multiple cyst-like, blood-filled cavities in the liver and spleen. Most cases of CSD can be prevented by keeping cats free of fleas and promptly cleaning a cat scratch with soap and warm water.

The diagnosis of CSD is difficult because the bacterium does not grow readily in the laboratory. When necessary, immunofluorescence, serological tests, PCR, and gene sequencing can be performed to identify the bacterial species. Given the limited nature of these infections, antibiotics are not normally prescribed. For immunocompromised patients, rifampin, azithromycin, ciprofloxacin, gentamicin (intramuscularly), or TMP-SMZ are generally the most effective options.

**Rat-Bite Fever**

The zoonotic infection **rat-bite fever** can be caused by two different gram-negative bacteria: *Streptobacillus moniliformis*, which is more common in North America, and *Spirillum minor*, which is more common in Asia. Because of modern sanitation efforts, rat bites are rare in the US. However, contact with fomites, food, or water contaminated by rat feces or body fluids can also cause infections. Signs and symptoms of rat-bite fever include fever, vomiting, myalgia (muscle pain), arthralgia (joint pain), and a maculopapular rash on the hands and feet. An ulcer may also form at the site of a bite, along with some swelling of nearby lymph nodes. In most cases, the infection is self-limiting. Little is known about the virulence factors that contribute to these signs and symptoms of disease.

Cell culture, MALDI-TOF mass spectrometry, PCR, or ELISA can be used in the identification of *Streptobacillus moniliformis*. The diagnosis *Spirillum minor* may be confirmed by direct microscopic observation of the pathogens in blood using Giemsa or Wright stains, or darkfield microscopy. Serological tests can be used to detect a host immune response to the pathogens after about 10 days. The most commonly used antibiotics to treat these infections are penicillin or doxycycline.

**Plague**

The gram-negative bacillus *Yersinia pestis* causes the zoonotic infection **plague**. This bacterium causes acute febrile disease in animals, usually rodents or other small mammals, and humans. The disease is associated with a high mortality rate if left untreated. Historically, *Y. pestis* has been responsible for several devastating pandemics, resulting in millions of deaths (see Micro Connections: The History of the Plague). There are three forms of plague: **bubonic plague** (the most common form, accounting for about 80% of cases), **pneumonic plague**, and **septicemic plague**. These forms are differentiated by the mode of transmission and the initial site of infection. Figure 25.9 illustrates these various modes of transmission and infection between animals and humans.

In bubonic plague, *Y. pestis* is transferred by the bite of infected fleas. Since most flea bites occur on the legs and ankles, *Y. pestis* is often introduced into the tissues and blood circulation in the lower extremities. After a 2- to 6-day incubation period, patients experience an abrupt onset fever (39.5–41 °C [103.1–105.8 °F]), headache, hypotension, and chills. The pathogen localizes in lymph nodes, where it causes inflammation, swelling, and hemorrhaging that results in purple buboes (Figure 25.10). Buboes often form in lymph nodes of the groin first because these are the nodes associated with the lower limbs; eventually, through circulation in the blood and lymph, lymph nodes throughout the body become infected and form buboes. The average mortality rate for bubonic plague is about 55% if untreated and about 10% with antibiotic treatment.

Septicemic plague occurs when *Y. pestis* is directly introduced into the bloodstream through a cut or wound and circulates through the body. The incubation period for septicemic plague is 1 to 3 days, after which patients develop fever, chills, extreme weakness, abdominal pain, and shock. Disseminated intravascular coagulation (DIC) can also occur, resulting in the formation of thrombi that obstruct blood vessels and promote ischemia and necrosis in surrounding tissues (Figure 25.10). Necrosis occurs most commonly in extremities such as fingers and toes, which become blackened. Septicemic plague can quickly lead to death, with a mortality rate near 100% when it is untreated. Even with antibiotic treatment, the mortality rate is about 50%.
Pneumonic plague occurs when *Y. pestis* causes an infection of the lungs. This can occur through inhalation of aerosolized droplets from an infected individual or when the infection spreads to the lungs from elsewhere in the body in patients with bubonic or septicemic plague. After an incubation period of 1 to 3 days, signs and symptoms include fever, headache, weakness, and a rapidly developing pneumonia with shortness of breath, chest pain, and cough producing bloody or watery mucus. The pneumonia may result in rapid respiratory failure and shock. Pneumonic plague is the only form of plague that can be spread from person to person by infectious aerosol droplet. If untreated, the mortality rate is near 100%; with antibiotic treatment, the mortality rate is about 50%.

**Figure 25.9** *Yersinia pestis*, the causative agent of plague, has numerous modes of transmission. The modes are divided into two ecological classes: urban and sylvatic (i.e., forest or rural). The urban cycle primarily involves transmission from infected urban mammals (rats) to humans by flea vectors (brown arrows). The disease may travel between urban centers (purple arrow) if infected rats find their way onto ships or trains. The sylvatic cycle involves mammals more common in nonurban environments. Sylvatic birds and mammals (including humans) may become infected after eating infected mammals (pink arrows) or by flea vectors. Pneumonic transmission occurs between humans or between humans and infected animals through the inhalation of *Y. pestis* in aerosols. (credit “diagram”: modification of work by Stenseth NC, Atshabar BB, Begon M, Belmain SR, Bertherat E, Carniel E, Gage KL, Leirs H, and Rahalison L; credit “cat”: modification of work by “KaCey97078”/Flickr)
Yersinia pestis infection can cause inflamed and swollen lymph nodes (buboes), like these in the groin of an infected patient. Septicemic plague caused necrotic toes in this patient. Vascular damage at the extremities causes ischemia and tissue death. (credit a: modification of work by American Society for Microbiology; credit b: modification of work by Centers for Disease Control and Prevention)

The high mortality rate for the plague is, in part, a consequence of it being unusually well equipped with virulence factors. To date, there are at least 15 different major virulence factors that have been identified from Y. pestis and, of these, eight are involved with adherence to host cells. In addition, the F1 component of the Y. pestis capsule is a virulence factor that allows the bacterium to avoid phagocytosis. F1 is produced in large quantities during mammalian infection and is the most immunogenic component. Successful use of virulence factors allows the bacilli to disseminate from the area of the bite to regional lymph nodes and eventually the entire blood and lymphatic systems.

Culturing and direct microscopic examination of a sample of fluid from a bubo, blood, or sputum is the best way to identify Y. pestis and confirm a presumptive diagnosis of plague. Specimens may be stained using either a Gram, Giemsa, Wright, or Wayson’s staining technique (Figure 25.11). The bacteria show a characteristic bipolar staining pattern, resembling safety pins, that facilitates presumptive identification. Direct fluorescent antibody tests (rapid test of outer-membrane antigens) and serological tests like ELISA can be used to confirm the diagnosis. The confirmatory method for identifying Y. pestis isolates in the US is bacteriophage lysis.

Prompt antibiotic therapy can resolve most cases of bubonic plague, but septicemic and pneumonic plague are more difficult to treat because of their shorter incubation stages. Survival often depends on an early and accurate diagnosis and an appropriate choice of antibiotic therapy. In the US, the most common antibiotics used to treat patients with plague are gentamicin, fluoroquinolones, streptomycin, levofloxacin, ciprofloxacin, and doxycycline.

This Wright's stain of a blood sample from a patient with plague shows the characteristic "safety pin" appearance of *Yersinia pestis*. (credit: modification of work by Centers for Disease Control and Prevention)

**Check Your Understanding**

- Compare bubonic plague, septicemic plague, and pneumonic plague.

**Micro Connections**

**The History of the Plague**

The first recorded pandemic of plague, the Justinian plague, occurred in the sixth century CE. It is thought to have originated in central Africa and spread to the Mediterranean through trade routes. At its peak, more than 5,000 people died per day in Constantinople alone. Ultimately, one-third of that city's population succumbed to plague. The impact of this outbreak probably contributed to the later fall of Emperor Justinian.

The second major pandemic, dubbed the Black Death, occurred during the 14th century. This time, the infections are thought to have originated somewhere in Asia before being transported to Europe by trade, soldiers, and war refugees. This outbreak killed an estimated one-quarter of the population of Europe (25 million, primarily in major cities). In addition, at least another 25 million are thought to have been killed in Asia and Africa. This second pandemic, associated with strain *Yersinia pestis* biovar Medievalis, cycled for another 300 years in Europe and Great Britain, and was called the Great Plague in the 1660s.

The most recent pandemic occurred in the 1890s with *Yersinia pestis* biovar Orientalis. This outbreak originated in the Yunnan province of China and spread worldwide through trade. It is at this time that plague made its way to the US. The etiologic agent of plague was discovered by Alexandre Yersin (1863–1943) during this outbreak as well. The overall number of deaths was lower than in prior outbreaks, perhaps because of improved sanitation and medical support. Most of the deaths attributed to this final pandemic occurred in India.

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Zoonotic Febrile Diseases

A wide variety of zoonotic febrile diseases (diseases that cause fever) are caused by pathogenic bacteria that require arthropod vectors. These pathogens are either obligate intracellular species of *Anaplasma*, *Bartonella*, *Ehrlichia*, *Orientia*, and *Rickettsia*, or spirochetes in the genus *Borrelia*. Isolation and identification of pathogens in this group are best performed in BSL-3 laboratories because of the low infective dose associated with the diseases.

**Anaplasmosis**

The zoonotic tickborne disease **human granulocytic anaplasmosis (HGA)** is caused by the obligate intracellular pathogen *Anaplasma phagocytophilum*. HGA is endemic primarily in the central and northeastern US and in countries in Europe and Asia.

HGA is usually a mild febrile disease that causes flu-like symptoms in immunocompetent patients; however, symptoms are severe enough to require hospitalization in at least 50% of infections and, of those patients, less than 1% will die of HGA. Small mammals such as white-footed mice, chipmunks, and voles have been identified as reservoirs of *A. phagocytophilum*, which is transmitted by the bite of an *Ixodes* tick. Five major virulence factors have been reported in *Anaplasma*; three are adherence factors and two are factors that allow the pathogen to avoid the human immune response. Diagnostic approaches include locating intracellular microcolonies of *Anaplasma* through microscopic examination of neutrophils or eosinophils stained with Giemsa or Wright stain, PCR for detection of *A. phagocytophilum*, and serological tests to detect antibody titers against the pathogens. The primary antibiotic used for treatment is doxycycline.

**Ehrlichiosis**

Human monocytotropic ehrlichiosis (HME) is a zoonotic tickborne disease caused by the BSL-2, obligate intracellular pathogen *Ehrlichia chaffeensis*. Currently, the geographic distribution of HME is primarily the eastern half of the US, with a few cases reported in the West, which corresponds with the known geographic distribution of the primary vector, the lone star tick (*Amblyomma americanum*). Symptoms of HME are similar to the flu-like symptoms observed in anaplasmosis, but a rash is more common, with 60% of children and less than 30% of adults developing petechial, macula, and maculopapular rashes. Virulence factors allow *E. chaffeensis* to adhere to and infect monocytes, forming intracellular microcolonies in monocytes that are diagnostic for the HME. Diagnosis of HME can be confirmed with PCR and serologic tests. The first-line treatment for adults and children of all ages with HME is doxycycline.
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. 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. 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.

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.

Murine (Endemic) Typhus

Murine typhus (also known as endemic typhus) is caused by *Rickettsia typhi* and is transmitted by the bite of the rat flea, *Xenopsylla cheopis*, with infected rats as the main reservoir. Clinical signs and symptoms of *murine typhus* include a rash and chills accompanied by headache and fever that last about 12 days. Some patients also exhibit a cough and pneumonia-like symptoms. Severe illness can develop in immunocompromised patients, with seizures, coma, and renal and respiratory failure.

Clinical diagnosis of murine typhus can be confirmed from a biopsy specimen from the rash. Diagnostic tests include indirect immunofluorescent antibody (IFA) staining, PCR for *R. typhi*, and acute and convalescent serologic testing. Primary treatment is doxycycline, with chloramphenicol as the second choice.

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. The map in Figure 25.12 shows the distribution of prevalence in the US in 2010.

Figure 25.12  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 25.13). 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 25.13  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 25.15). 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.\(^{24}\)

*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 25.14).

The symptoms of Lyme disease follow three stages: early localized, early disseminated, and late stage. During the early-localized stage, approximately 70%–80%\(^\text{[25]}\) 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 25.15)\(^\text{[26]}\). 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 25.15). In addition, indirect

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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 25.15  (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 25.16). For louseborne relapsing fever, doxycycline or erythromycin are the first-line antibiotics. For tickborne relapsing fever, tetracycline or erythromycin are the first-line antibiotics.
Trench Fever

The louseborne disease trench fever was first characterized as a specific disease during World War I, when approximately 1 million soldiers were infected. Today, it is primarily limited to areas of the developing world where poor sanitation and hygiene lead to infestations of lice (e.g., overpopulated urban areas and refugee camps). Trench fever is caused by the gram-negative bacterium Bartonella quintana, which is transmitted when feces from infected body lice, Pediculus humanus var corporis, are rubbed into the louse bite, abraded skin, or the conjunctiva. The symptoms typically follow a 5-day course marked by a high fever, body aches, conjunctivitis, ocular pain, severe headaches, and severe bone pain in the shins, neck, and back. Diagnosis can be made using blood cultures; serological tests like ELISA can be used to detect antibody titers to the pathogen and PCR can also be used. The first-line antibiotics are doxycycline, macrolide antibiotics, and ceftriaxone.

Check Your Understanding

- What is the vector associated with epidemic typhus?
- Describe the life cycle of the deer tick and how it spreads Lyme disease.

Micro Connections

Tick Tips

Many of the diseases covered in this chapter involve arthropod vectors. Of these, ticks are probably the most commonly encountered in the US. Adult ticks have eight legs and two body segments, the cephalothorax and the head (Figure 25.17). They typically range from 2 mm to 4 mm in length, and feed on the blood of the host by attaching themselves to the skin.

Unattached ticks should be removed and eliminated as soon as they are discovered. When removing a tick that has already attached itself, keep the following guidelines in mind to reduce the chances of exposure to pathogens:
• Use blunt tweezers to gently pull near the site of attachment until the tick releases its hold on the skin.
• Avoid crushing the tick’s body and do not handle the tick with bare fingers. This could release bacterial pathogens and actually increase your exposure. The tick can be killed by drowning in water or alcohol, or frozen if it may be needed later for identification and analysis.
• Disinfect the area thoroughly by swabbing with an antiseptic such as isopropanol.
• Monitor the site of the bite for rashes or other signs of infection.

Many ill-advised home remedies for tick removal have become popular in recent years, propagated by social media and pseudojournalism. Health professionals should discourage patients from resorting to any of the following methods, which are NOT recommended:

• using chemicals (e.g., petroleum jelly or fingernail polish) to dislodge an attached tick, because it can cause the tick to release fluid, which can increase the chance of infection
• using hot objects (matches or cigarette butts) to dislodge an attached tick
• squeezing the tick’s body with fingers or tweezers

Figure 25.17  (a) This black-legged tick, also known as the deer tick, has not yet attached to the skin. (b) A notched tick extractor can be used for removal. (c) To remove an attached tick with fine-tipped tweezers, pull gently on the mouth parts until the tick releases its hold on the skin. Avoid squeezing the tick’s body, because this could release pathogens and thus increase the risk of contracting Lyme disease. (credit a: modification of work by Jerry Kirkhart; credit c: modification of work by Centers for Disease Control and Prevention)

**Disease Profile**

**Bacterial Infections of the Circulatory and Lymphatic Systems**

Although the circulatory system is a closed system, bacteria can enter the bloodstream through several routes. Wounds, animal bites, or other breaks in the skin and mucous membranes can result in the rapid dissemination of bacterial pathogens throughout the body. Localized infections may also spread to the bloodstream, causing serious and often fatal systemic infections. **Figure 25.18** and **Figure 25.19** summarize the major characteristics of bacterial infections of the circulatory and lymphatic systems.
### Bacterial Infections of the Circulatory and Lymphatic Systems

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<td>Endocarditis pericarditis</td>
<td><em>S. pyogenes</em>, <em>Streptococcus spp.</em>, <em>Enterococcus spp.</em>, <em>HACEK bacilli</em></td>
<td>Chest pain, difficulty breathing, dry cough, fever; potentially fatal damage to heart valves</td>
<td>Pathogens introduced to bloodstream via contaminated catheters, dental procedures, piercings, or wounds</td>
<td>Echocardiogram, blood culture</td>
<td>Ampicillin, nafcillin, gentamicin, others; based on susceptibility testing</td>
</tr>
<tr>
<td>Epidemic typhus</td>
<td><em>Rickettsia prowazekii</em></td>
<td>High fever, body aches, rash; potentially fatal damage to heart and brain</td>
<td>From rodent reservoir via body louse vector</td>
<td>PCR, immunofluorescence</td>
<td>Doxycycline, chloramphenicol</td>
</tr>
<tr>
<td>Gas gangrene</td>
<td><em>Clostridium perfringens</em>, other <em>Clostridium spp.</em></td>
<td>Rapidly spreading myonecrosis, edema, yellowish and then purple discharge from wound, pockets of gas in tissues, septic shock and death</td>
<td>Germination of endospores in ischemic tissues, typically due to injury or chronic disease (e.g., diabetes)</td>
<td>Wound culture</td>
<td>Penicillin G, clindamycin, metronidazole</td>
</tr>
<tr>
<td>Infectious arthritis (septic arthritis)</td>
<td><em>Staphylococcus aureus</em>, <em>Neisseria gonorrhoeae</em></td>
<td>Joint pain and swelling, limited range of motion</td>
<td>Infection spreads to joint via circulatory system from wound or surgical site</td>
<td>Synovial fluid culture</td>
<td>Oxacillin, cefazolin, ceftriaxone</td>
</tr>
<tr>
<td>Lyme disease</td>
<td><em>Borrelia burgdorferi</em></td>
<td>Early localized: bull’s eye rash, malaise, headache, fever, muscle stiffness; early disseminated: stiff neck, facial paralysis, arthritis, carditis; late-stage: arthritis, meningitis, possibly fatal</td>
<td>From deer, rodent, bird reservoirs via tick vector</td>
<td>IFA, serology, and ELISA</td>
<td>Amoxicillin, doxycycline, penicillin G, chloramphenicol, ceftriaxone</td>
</tr>
<tr>
<td>Murine (endemic) typhus</td>
<td><em>Rickettsia typhi</em></td>
<td>Low-grade fever, rash, headache, cough</td>
<td>From rodents or between humans via rat flea vector</td>
<td>Biopsy, IFA, PCR</td>
<td>Doxycycline, chloramphenicol</td>
</tr>
<tr>
<td>Osteomyelitis</td>
<td><em>Staphylococcus aureus</em>, <em>Streptococcus pyogenes</em>, others</td>
<td>Inflammation of bone tissue, leading to fever, localized pain, edema, ulcers, bone loss</td>
<td>Pathogens introduced through trauma, prothetic joint replacement, or from other infected body site via bloodstream</td>
<td>Radiograph of affected bone, culture of bone biopsy specimen</td>
<td>Cephalosporin, penicillins, others</td>
</tr>
</tbody>
</table>

**Figure 25.18**
## Bacterial Infections of the Circulatory and Lymphatic Systems (continued)

<table>
<thead>
<tr>
<th>Disease</th>
<th>Pathogen</th>
<th>Signs and Symptoms</th>
<th>Transmission</th>
<th>Diagnostic Tests</th>
<th>Antimicrobial Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plague</td>
<td>Yersinia pestis</td>
<td>Bubonic: buboes, fever, internal hemorrhaging; septicemic: fever, abdominal pain, shock, DIC, necrosis in extremities; pneumonic: acute pneumonia, respiratory failure, shock. All forms have high mortality rates.</td>
<td>Transmitted from mammal reservoirs via flea vectors or consumption of infected animal; transmission of pneumonic plague between humans via respiratory aerosols</td>
<td>Culture of bacteria from lymph, blood, or sputum samples; DFA, ELISA</td>
<td>Gentamycin, fluoroquinolones, others</td>
</tr>
<tr>
<td>Puerperal sepsis</td>
<td>Streptococcus pyogenes, many others</td>
<td>Rapid-onset fever, shock, and death</td>
<td>Pathogens introduced during or immediately following childbirth</td>
<td>Wound, urine, or blood culture</td>
<td>As determined by susceptibility testing</td>
</tr>
<tr>
<td>Rat-bite fever</td>
<td>Streptobacillus moniliformis, Spirillum minor</td>
<td>Fever, muscle and joint pain, rash, ulcer</td>
<td>Bite from infected rat or exposure to rat feces or body fluids in contaminated food or water</td>
<td>Observation of the organism from samples and antibody tests</td>
<td>Penicillin</td>
</tr>
<tr>
<td>Relapsing fever</td>
<td>Borrelia recurrentis, B. hermsii, other Borrelia spp.</td>
<td>Recurring fever, headache, muscle aches</td>
<td>From rodent or human reservoir via body louse or tick vector</td>
<td>Darkfield microscopy</td>
<td>Doxycycline, tetracycline, erythromycin</td>
</tr>
<tr>
<td>Rheumatic fever</td>
<td>Streptococcus pyogenes</td>
<td>Joint pain and swelling, inflammation and scarring of heart valves, heart murmur</td>
<td>Sequela of streptococcal pharyngitis</td>
<td>Serology, electrocardiogram, echocardiogram</td>
<td>Benzathine benzylpenicillin</td>
</tr>
<tr>
<td>Rocky Mountain spotted fever</td>
<td>Rickettsia rickettsii</td>
<td>High fever, headache, body aches, nausea and vomiting, petechial rash; potentially fatal hypotension and ischemia due to blood coagulation</td>
<td>From rodent reservoir via tick vectors</td>
<td>Biopsy, serology, PCR</td>
<td>Doxycycline, chloramphenicol</td>
</tr>
<tr>
<td>Toxic shock syndrome (TSS)</td>
<td>Staphylococcus aureus</td>
<td>Sudden high fever, vomiting, diarrhea, hypotension, death</td>
<td>Pathogens from localized infection spread to bloodstream; pathogens introduced on tampons or other intravaginal products</td>
<td>Serology, toxin identification from isolates</td>
<td>Clindamycin, vancomycin</td>
</tr>
<tr>
<td>Toxic shock-like syndrome (STSS)</td>
<td>Streptococcus pyogenes</td>
<td>Sudden high fever, vomiting, diarrhea, acute respiratory distress syndrome (ARDS), hypoxemia, necrotizing fasciitis, death</td>
<td>Sequela of streptococcal skin or soft-tissue infection</td>
<td>Serology, blood culture, urinalysis</td>
<td>Penicillin, cefaloスポリン</td>
</tr>
<tr>
<td>Trench fever</td>
<td>Bartonella quintana</td>
<td>High fever, conjunctivitis, ocular pain, headaches, severe pain in bones of shins, neck, and back</td>
<td>Between humans via body louse vector</td>
<td>Blood culture, ELISA, PCR</td>
<td>Doxycycline, macroside antibiotics, ceftriaxone</td>
</tr>
<tr>
<td>Tularemia (rabbit fever)</td>
<td>Francisella tularensis</td>
<td>Skin lesions, fever, chills, headache, buboes</td>
<td>Eating or handling infected rabbit: transmission from infected animal via tick or fly vector; aerosol transmission (in laboratory or as bioweapon)</td>
<td>DFA</td>
<td>Streptomycin, gentamycin, others</td>
</tr>
</tbody>
</table>

Figure 25.19
25.3 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.

Infectious Mononucleosis and Burkitt Lymphoma

Human herpesvirus 4, also known as Epstein-Barr virus (EBV), has been associated with a variety of human diseases, such as mononucleosis and Burkitt lymphoma. Exposure to the human herpesvirus 4 (HHV-4) is widespread and nearly all people have been exposed at some time in their childhood, as evidenced by serological tests on populations. The virus primarily resides within B lymphocytes and, like all herpes viruses, can remain dormant in a latent state for a long time.

When uninfected young adults are exposed to EBV, they may experience infectious mononucleosis. The virus is mainly spread through contact with body fluids (e.g., saliva, blood, and semen). The main symptoms include pharyngitis, fever, fatigue, and lymph node swelling. Abdominal pain may also occur as a result of spleen and liver enlargement in the second or third week of infection. The disease typically is self-limiting after about a month. The main symptom, extreme fatigue, can continue for several months, however. Complications in immunocompetent patients are rare but can include jaundice, anemia, and possible rupture of the spleen caused by enlargement.

In patients with malaria or HIV, Epstein-Barr virus can lead to a fast-growing malignant cancer known as Burkitt lymphoma (Figure 25.20). This condition is a form of non-Hodgkin lymphoma that produces solid tumors chiefly consisting of aberrant B cells. Burkitt lymphoma is more common in Africa, where prevalence of HIV and malaria is high, and it more frequently afflicts children. Repeated episodes of viremia caused by reactivation of the virus are common in immunocompromised individuals. In some patients with AIDS, EBV may induce the formation of malignant B-cell lymphomas or oral hairy leukoplakia. Immunodeficiency-associated Burkitt lymphoma primarily occurs in patients with HIV. HIV infection, similar to malaria, leads to polyclonal B-cell activation and permits poorly controlled proliferation of EBV+ B cells, leading to the formation of lymphomas.

Infectious mononucleosis is typically diagnosed based on the initial clinical symptoms and a test for antibodies to EBV-associated antigens. Because the disease is self-limiting, antiviral treatments are rare for mononucleosis. Cases of Burkitt lymphoma are diagnosed from a biopsy specimen from a lymph node or tissue from a suspected tumor. Staging of the cancer includes computed tomography (CT) scans of the chest, abdomen, pelvis, and cytologic and histologic evaluation of biopsy specimens. Because the tumors grow so rapidly, staging studies must be expedited and treatment must be initiated promptly. An intensive alternating regimen of cyclophosphamide, vincristine, doxorubicin, methotrexate, ifosfamide, etoposide, and cytarabine (CODOX-M/IVAC) plus rituximab results in a cure rate greater than 90% for children and adults.
Cytomegalovirus Infections

Also known as cytomegalovirus (CMV), human herpesvirus 5 (HHV-5) is a virus with high infection rates in the human population. It is currently estimated that 50% of people in the US have been infected by the time they reach adulthood.\(^{[27]}\) CMV is the major cause of non-Epstein-Barr infectious mononucleosis in the general human population. It is also an important pathogen in immunocompromised hosts, including patients with AIDS, neonates, and transplant recipients. However, the vast majority of CMV infections are asymptomatic. In adults, if symptoms do occur, they typically include fever, fatigue, swollen glands, and pharyngitis.

CMV can be transmitted between individuals through contact with body fluids such as saliva or urine. Common modes of transmission include sexual contact, nursing, blood transfusions, and organ transplants. In addition, pregnant women with active infections frequently pass this virus to their fetus, resulting in congenital CMV infections, which occur in approximately one in every 150 infants in US.\(^{[28]}\) Infants can also be infected during passage through the birth canal or through breast milk and saliva from the mother.

Perinatal infections tend to be milder but can occasionally cause lung, spleen, or liver damage. Serious symptoms in newborns include growth retardation, jaundice, deafness, blindness, and mental retardation if the virus crosses the placenta during the embryonic state when the body systems are developing in utero. However, a majority (approximately 80%) of infected infants will never have symptoms or experience long-term problems.\(^{[29]}\) Diagnosis of CMV infection during pregnancy is usually achieved by serology; CMV is the “C” in prenatal TORCH screening.

Many patients receiving blood transfusions and nearly all those receiving kidney transplants ultimately become infected with CMV. Approximately 60% of transplant recipients will have CMV infection and more than 20% will develop symptomatic disease.\(^{[30]}\) These infections may result from CMV-contaminated tissues but also may be a consequence of immunosuppression required for transplantation causing reactivation of prior CMV infections. The resulting viremia can lead to fever and leukopenia, a decrease in the number of white blood cells in the bloodstream.

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29. ibid.
Serious consequences may include liver damage, transplant rejection, and death. For similar reasons, many patients with AIDS develop active CMV infections that can manifest as encephalitis or progressive retinitis leading to blindness.\(^{[31]}\)

Diagnosis of a localized CMV infection can be achieved through direct microscopic evaluation of tissue specimens stained with routine stains (e.g., Wright-Giemsa, hematoxylin and eosin, Papanicolaou) and immunohistochemical stains. Cells infected by CMV produce characteristic inclusions with an "owl's eye" appearance; this sign is less sensitive than molecular methods like PCR but more predictive of localized disease (Figure 25.21). For more severe CMV infection, tests such as enzyme immunoassay (EIA), indirect immunofluorescence antibody (IFA) tests, and PCR, which are based on detection of CMV antigen or DNA, have a higher sensitivity and can determine viral load. Cultivation of the virus from saliva or urine is still the method for detecting CMV in newborn babies up to 3 weeks old. Ganciclovir, valganciclovir, foscarnet, and cidofovir are the first-line antiviral drugs for serious CMV infections.

**Figure 25.21** Cells infected with CMV become enlarged and have a characteristic "owl's eye" nucleus. This micrograph shows kidney cells from a patient with CMV. (credit: modification of work by Centers for Disease Control and Prevention)

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**Check Your Understanding**

- Compare the diseases caused by HHV-4 and HHV-5.

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**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.\(^{[32]}\) 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.[33]

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.[34] 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.

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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. 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.

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.

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Check Your Understanding

- Name three arboviral diseases and explain why they are so named.
- What is the best method for controlling outbreaks of arboviral diseases?

Ebola Virus Disease

The Ebola virus disease (EVD) is a highly contagious disease caused by species of *Ebolavirus*, a BSL-4 filovirus (Figure 25.22). 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.\(^\text{37}\)

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.

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%. 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%.

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.

**Check Your Understanding**

- Compare the two Hantavirus diseases discussed in this section.

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39. ibid.
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 25.23) 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.[41] Sub-Saharan Africa also accounts for two-thirds of the global total of new HIV infections (Figure 25.24).[42]

Figure 25.23  This micrograph shows HIV particles (green) budding from a lymphocyte (top right). (credit: modification of work by Centers for Disease Control and Prevention)

42. ibid.
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 25.25).

- **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 25.25  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.

Check Your Understanding

- Why is it not yet possible to cure HIV infections?
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?

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 25.26.
<table>
<thead>
<tr>
<th>Disease</th>
<th>Pathogen</th>
<th>Signs and Symptoms</th>
<th>Transmission</th>
<th>Diagnostic Tests</th>
<th>Antimicrobial Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIDS/HIV infection</td>
<td>Human immunodeficiency virus (HIV)</td>
<td>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</td>
<td>Contact with body fluids (e.g., sexual contact, use of contaminated needles)</td>
<td>Serological tests for antibodies and/or HIV antigens; nucleic acid test (NAT) for presence of virus</td>
<td>Antiretroviral therapy (ART) using various combinations of drugs</td>
</tr>
<tr>
<td>Burkitt lymphoma</td>
<td>Epstein-Barr virus (human herpesvirus-4 [HHV-4])</td>
<td>Rapid formation of malignant B-cell tumors, oral hairy leukoplakia; fatal if not promptly treated</td>
<td>Contact with body fluids (e.g., saliva, blood, semen); primarily affects patients immunocompromised by HIV or malaria</td>
<td>CT scans, tumor biopsy</td>
<td>Intensive alternating chemotherapy regimen</td>
</tr>
<tr>
<td>Chikungunya fever</td>
<td>Chikungunya virus</td>
<td>Fever, rash, joint pain</td>
<td>Transmitted between humans by <em>Aedes aegypti</em> and <em>A. albopictus</em> vectors</td>
<td>Viral culture, IFA, EIA, ELISA, PCR, RT-PCR</td>
<td>None</td>
</tr>
<tr>
<td>Cytomegalovirus infection</td>
<td>Cytomegalovirus (HHV-5)</td>
<td>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</td>
<td>Contact with body fluids, blood transfusions, organ transplants; infected mothers can transmit virus to fetus transplacentally or to newborn in breastmilk, saliva</td>
<td>Histology, culture, IFA, IFA, PCR</td>
<td>Ganciclovir, valganciclovir, foscarnet, cidovir</td>
</tr>
<tr>
<td>Dengue fever (breakbone fever)</td>
<td>Dengue fever viruses 1–4</td>
<td>Fever, headache, extreme bone and joint pain, abdominal pain, vomiting, hemorrhaging; can be fatal</td>
<td>Transmitted between humans by <em>A. aegypti</em> and <em>A. albopictus</em> vectors</td>
<td>Serologic testing, ELISA, and PCR</td>
<td>None</td>
</tr>
<tr>
<td>Ebola virus disease (EVD)</td>
<td>Ebola virus</td>
<td>Fever, headache, joint pain, diarrhea, vomiting, hemorrhaging in gastrointestinal tract, organ failure; often fatal</td>
<td>Contact with body fluids (e.g., blood, saliva, sweat, urines, feces, vomit); highly contagious</td>
<td>ELISA, IgM ELISA, PCR, virus isolation</td>
<td>None</td>
</tr>
<tr>
<td>Hantavirus pulmonary syndrome (HPS)</td>
<td>Hantavirus</td>
<td>Initial flu-like symptoms followed by pulmonary edema and hypotension leading to pneumonia and shock; can be fatal</td>
<td>Inhalation of dried feces, urine from infected mouse or rat</td>
<td>ELISA, Western blot, RT-PCR</td>
<td>None</td>
</tr>
<tr>
<td>Hemorrhagic fever with renal syndrome</td>
<td>Hantavirus</td>
<td>Fever, headache, nausea, rash, or eye inflammation, followed by hemorrhaging and kidney failure; can be fatal</td>
<td>Inhalation of dried feces, urine from infected mouse or rat</td>
<td>ELISA, Western blot, RT-PCR</td>
<td>None</td>
</tr>
<tr>
<td>Infectious mononucleosis</td>
<td>Epstein-Barr virus (HHV-4), cytomegalovirus (HHV-5)</td>
<td>Pharyngitis, fever, extreme fatigue; swelling of lymph nodes, spleen, and liver</td>
<td>Contact with body fluids (e.g., saliva, blood, semen)</td>
<td>Tests for antibodies to various EBV-associated antigens</td>
<td>None</td>
</tr>
<tr>
<td>Yellow fever</td>
<td>Yellow fever virus</td>
<td>Dizziness, fever, chills, headache, myalgia, nausea, vomiting, constipation, fatigue; moderate to severe cases may include jaundice, rash, mucousal hemorrhaging, seizures, shock, and death</td>
<td>From monkeys to humans or between humans via <em>Aedes</em> or <em>Haemagogus</em> mosquito vectors</td>
<td>Culture, serology, PCR</td>
<td>None for treatment; preventive vaccine available</td>
</tr>
</tbody>
</table>
25.4 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. 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 25.27). 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 25.28). 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 25.27](image_url) The life cycle of *Plasmodium*. (credit: modification of work by Centers for Disease Control and Prevention)
Figure 25.28  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**

Visit this site ([https://openstax.org/l/22plasmodium](https://openstax.org/l/22plasmodium)) to learn how the parasite *Plasmodium* infects red blood cells.

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 ([https://openstax.org/l/22mosquitonet](https://openstax.org/l/22mosquitonet)) to learn more about their efforts to prevent malaria.

**Check Your Understanding**

- 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,[44] 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.[45] 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[46] (Figure 25.29).

*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.[47] 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.[48] 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 25.30).

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.

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47. Ibid
Figure 25.29  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 25.30  (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)

Check Your Understanding

• 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 25.31). 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.
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 25.32). 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. 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.

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 tissues of the heart and central nervous system. The disease can become chronic, with symptoms such as an enlarged liver and spleen, heart disease, and altered mental status. Over time, some patients can develop dilated cardiomyopathy, which can lead to heart failure.

Figure 25.31  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)


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 \textit{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.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fig25.32}
\caption{(a) \textit{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)}
\end{figure}

\section*{Check Your Understanding}

- How do kissing bugs infect humans with \textit{Trypanosoma cruzi}?

\section*{Leishmaniasis}

Although it is classified as an NTD, \textit{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 \textit{Leishmania}, protozoan parasites that are transmitted by sand fly vectors such as \textit{Phlebotomus} spp. and \textit{Lutzomyia} spp. Dogs, cats, sheep, horses, cattle rodents, and humans can all serve as reservoirs.

The \textit{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 25.33**).

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.

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**Figure 25.33**  
(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)
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.[51]

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 5.22).

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.

Check Your Understanding

- How do schistosome infections in humans occur?
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 25.34.
<table>
<thead>
<tr>
<th>Disease</th>
<th>Pathogen</th>
<th>Signs and Symptoms</th>
<th>Transmission</th>
<th>Diagnostic Tests</th>
<th>Antimicrobial Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Protozoa</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Babesiosis</td>
<td><em>Babesia</em> spp.</td>
<td>Malaise, chills, fever, headache, myalgia, arthralgia</td>
<td>From animals to humans via <em>Ixodes</em> tick vectors</td>
<td>Blood smear, serology, IFA, and PCR</td>
<td>Atovaquone and azithromycin or clindamycin and quinine</td>
</tr>
<tr>
<td>Chagas disease</td>
<td><em>Trypanosoma</em></td>
<td>Fever, headache, body aches, swollen lymph nodes;</td>
<td>Between humans or from animal reservoirs via triatomine (kissing bug) vector</td>
<td>Blood smear, IFA, EIA, PCR, xenodiagnosis</td>
<td>Nifurtimox, benznidazole</td>
</tr>
<tr>
<td></td>
<td><em>cruzi</em></td>
<td>potentially fatal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leishmaniasis</td>
<td><em>Leishmania</em> spp.</td>
<td>Ulcer; enlargement of the lymph nodes, liver, spleen,</td>
<td>Between humans or from animal reservoirs via sand fly (<em>Phlebotomus</em> spp., <em>Lutzomyia</em> spp.) vectors</td>
<td>Blood smear, culture, PCR, DNA probe, biopsy</td>
<td>Stibogluconate, amphotericin B.</td>
</tr>
<tr>
<td>Malaria</td>
<td><em>Plasmodium</em></td>
<td>Extreme fever, chills, myalgia, nausea, and vomiting,</td>
<td>Between humans via <em>Anopheles</em> mosquito vectors</td>
<td>Blood smear, EIA</td>
<td>Chloroquine, atovaquone, artesunate, and lumezantrine</td>
</tr>
<tr>
<td></td>
<td><em>vivax,</em> <em>P. malariae,</em> <em>P. falciparum,</em> <em>P. ovale,</em> <em>P. knowlesi</em></td>
<td>possibly leading to organ failure and death</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Toxoplasmosis</td>
<td><em>Toxoplasma</em></td>
<td>Tissue cysts; in pregnant women, birth defects or</td>
<td>Contact with feces of infected cat; eating contaminated vegetables or undercooked meat of infected animal</td>
<td>Serological tests, direct detection of pathogen in tissue sections</td>
<td>Sulfadiazine, pyrimethamine, spiramycin</td>
</tr>
<tr>
<td></td>
<td><em>gondii</em></td>
<td>miscarriage</td>
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<tr>
<td><strong>Helminths</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Schistosomiasis</td>
<td><em>Schistosoma</em></td>
<td>Rash, fever, chills, myalgia; chronic inflammation and scarring of liver, spleen, and other organs where cysts develop</td>
<td>Snail hosts release cercaria into freshwater; cercaria burrow into skin of swimmers and bathers</td>
<td>Eggs in stool or urine, tissue biopsy, serological testing</td>
<td>Praziquantel</td>
</tr>
</tbody>
</table>

*Figure 25.34*
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.\(^{[52]}\)

Summary

25.1 Anatomy of the Circulatory and Lymphatic Systems

- The **circulatory system** moves blood throughout the body and has no normal microbiota.
- The **lymphatic system** moves fluids from the interstitial spaces of tissues toward the circulatory system and filters the lymph. It also has no normal microbiota.
- The circulatory and lymphatic systems are home to many components of the host immune defenses.
- Infections of the circulatory system may occur after a break in the skin barrier or they may enter the bloodstream at the site of a localized infection. Pathogens or toxins in the bloodstream can spread rapidly throughout the body and can provoke systemic and sometimes fatal inflammatory responses such as **SIRS**, **sepsis**, and **endocarditis**.
- Infections of the lymphatic system can cause **lymphangitis** and **lymphadenitis**.

25.2 Bacterial Infections of the Circulatory and Lymphatic Systems

- 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**, **rheumatic fever**, **endocarditis**, **gas gangrene**, and **osteomyelitis**, and **toxic shock syndrome** are typically a result of injury or introduction of bacteria by medical or surgical intervention.
- **Tularemia**, **brucellosis**, **cat-scratch fever**, **rat-bite fever**, and **bubonic plague** are zoonotic diseases transmitted by biological vectors.
- **Ehrlichiosis**, **anaplasmosis**, **endemic** and **murine typhus**, **Rocky Mountain spotted fever**, **Lyme disease**, **relapsing fever**, and **trench fever** are transmitted by arthropod vectors.

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• 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.

25.3 Viral Infections of the Circulatory and Lymphatic Systems
• Human herpesviruses such as Epstein-Barr virus (HHV-4) and cytomegalovirus (HHV-5) are widely distributed. The former is associated with infectious mononucleosis and Burkitt lymphoma, and the latter can cause serious congenital infections as well as serious disease in immunocompromised adults.
• Arboviral diseases such as yellow fever, dengue fever, and chikungunya fever are characterized by high fevers and vascular damage that can often be fatal. Ebola virus disease is a highly contagious and often fatal infection spread through contact with bodily fluids.
• Although there is a vaccine available for yellow fever, treatments for patients with yellow fever, dengue, chikungunya fever, and Ebola virus disease are limited to supportive therapies.
• 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.
• Vector control and animal reservoir control remain the best defenses against most viruses that cause diseases of the circulatory system.

25.4 Parasitic Infections of the Circulatory and Lymphatic Systems
• 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.

Review Questions

Multiple Choice
1. Which term refers to an inflammation of the blood vessels?
   a. lymphangitis
   b. endocarditis
   c. pericarditis
   d. vasculitis

2. Which of the following is located in the interstitial spaces within tissues and releases nutrients, immune factors, and oxygen to those tissues?
   a. lymphatics
   b. arterioles
   c. capillaries
   d. veins
3. Which of these conditions results in the formation of a bubo?
   a. lymphangitis
   b. lymphadenitis
   c. ischemia
   d. vasculitis

4. Which of the following is where are most microbes filtered out of the fluids that accumulate in the body tissues?
   a. spleen
   b. lymph nodes
   c. pericardium
   d. blood capillaries

5. Which of the following diseases is caused by a spirochete?
   a. tularemia
   b. relapsing fever
   c. rheumatic fever
   d. Rocky Mountain spotted fever

6. Which of the following diseases is transmitted by body lice?
   a. tularemia
   b. bubonic plague
   c. murine typhus
   d. epidemic typhus

7. What disease is most associated with Clostridium perfringens?
   a. endocarditis
   b. osteomyelitis
   c. gas gangrene
   d. rat bite fever

8. Which bacterial pathogen causes plague?
   a. Yersinia pestis
   b. Bacillus moniliformis
   c. Bartonella quintana
   d. Rickettsia rickettsii

9. Which of the following viruses is most widespread in the human population?
   a. human immunodeficiency virus
   b. Ebola virus
   c. Epstein-Barr virus
   d. hantavirus

10. Which of these viruses is spread through mouse urine or feces?
    a. Epstein-Barr
    b. hantavirus
    c. human immunodeficiency virus
    d. cytomegalovirus

11. 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

12. Which of the following diseases is caused by a helminth?
    a. leishmaniasis
    b. malaria
    c. Chagas disease
    d. schistosomiasis

13. Which of these is the most common form of leishmaniasis?
    a. cutaneous
    b. mucosal
    c. visceral
    d. intestinal

14. Which of the following is a causative agent of malaria?
    a. Trypanosoma cruzi
    b. Toxoplasma gondii
    c. Plasmodium falciparum
    d. Schistosoma mansoni

15. Which of the following diseases does not involve an arthropod vector?
    a. schistosomiasis
    b. malaria
    c. Chagas disease
    d. babesiosis
Fill in the Blank
16. Vasculitis can cause blood to leak from damaged vessels, forming purple spots called ________.
17. The lymph reenters the vascular circulation at ________.
18. Lyme disease is characterized by a(n) ________ that forms at the site of infection.
19. ________ refers to a loss of blood pressure resulting from a system-wide infection.
20. ________ is a cancer that forms in patients with HHV-4 and malaria coinfections.
21. ________ are transmitted by vectors such as ticks or mosquitoes.
22. Infectious mononucleosis is caused by ________ infections.
23. The ________ mosquito is the biological vector for malaria.
24. The kissing bug is the biological vector for ________.
25. Cercarial dermatitis is also known as ________.

Short Answer
26. How do lymph nodes help to maintain a microbial-free circulatory and lymphatic system?
27. What are the three forms of plague and how are they contracted?
28. Compare epidemic and murine typhus.
29. Describe the progression of an HIV infection over time with regard to the number of circulating viruses, host antibodies, and CD4 T cells.
30. Describe the general types of diagnostic tests used to diagnose patients infected with HIV.
31. Identify the general categories of drugs used in ART used to treat patients infected with HIV.
32. Describe main cause of *Plasmodium falciparum* infection symptoms.
33. Why should pregnant women avoid cleaning their cat’s litter box or do so with protective gloves?

Critical Thinking
34. What term refers to the red streaks seen on this patient’s skin? What is likely causing this condition?

![Figure 25.35](credit: modification of work by Centers for Disease Control and Prevention)

35. Why would septicemia be considered a more serious condition than bacteremia?
36. Why are most vascular pathogens poorly communicable from person to person?
37. How have human behaviors contributed to the spread or control of arthropod-borne vascular diseases?
38. Which is a bigger threat to the US population, Ebola or yellow fever? Why?
39. What measures can be taken to reduce the likelihood of malaria reemerging in the US?
Chapter 26

Nervous System Infections

Figure 26.1  This dog is exhibiting the restlessness and aggression associated with rabies, a neurological disease that frequently affects mammals and can be transmitted to humans. (credit: modification of work by the Centers for Disease Control and Prevention)

Chapter Outline

26.1 Anatomy of the Nervous System
26.2 Bacterial Diseases of the Nervous System
26.3 Acellular Diseases of the Nervous System
26.4 Fungal and Parasitic Diseases of the Nervous System

Introduction

Few diseases inspire the kind of fear that rabies does. The name is derived from the Latin word for “madness” or “fury,” most likely because animals infected with rabies may behave with uncharacteristic rage and aggression. And while the thought of being attacked by a rabid animal is terrifying enough, the disease itself is even more frightful. Once symptoms appear, the disease is almost always fatal, even when treated.

Rabies is an example of a neurological disease caused by an acellular pathogen. The rabies virus enters nervous tissue shortly after transmission and makes its way to the central nervous system, where its presence leads to changes in behavior and motor function. Well-known symptoms associated with rabid animals include foaming at the mouth, hydrophobia (fear of water), and unusually aggressive behavior. Rabies claims tens of thousands of human lives worldwide, mainly in Africa and Asia. Most human cases result from dog bites, although many mammal species can become infected and transmit the disease. Human infection rates are low in the United States and many other countries as a result of control measures in animal populations. However, rabies is not the only disease with serious or fatal neurological effects. In this chapter, we examine the important microbial diseases of the nervous system.
26.1 Anatomy of the Nervous System

Learning Objectives

- Describe the major anatomical features of the nervous system
- Explain why there is no normal microbiota of the nervous system
- Explain how microorganisms overcome defenses of the nervous system to cause infection
- Identify and describe general symptoms associated with various infections of the nervous system

The human nervous system can be divided into two interacting subsystems: the peripheral nervous system (PNS) and the central nervous system (CNS). The CNS consists of the brain and spinal cord. The peripheral nervous system is an extensive network of nerves connecting the CNS to the muscles and sensory structures. The relationship of these systems is illustrated in Figure 26.2.

The Central Nervous System

The brain is the most complex and sensitive organ in the body. It is responsible for all functions of the body, including serving as the coordinating center for all sensations, mobility, emotions, and intellect. Protection for the brain is provided by the bones of the skull, which in turn are covered by the scalp, as shown in Figure 26.3. The scalp is composed of an outer layer of skin, which is loosely attached to the aponeurosis, a flat, broad tendon layer that anchors the superficial layers of the skin. The periosteum, below the aponeurosis, firmly encases the bones of the skull and provides protection, nutrition to the bone, and the capacity for bone repair. Below the boney layer of the skull are three layers of membranes called meninges that surround the brain. The relative positions of these meninges are shown in Figure 26.3. The meningeal layer closest to the bones of the skull is called the dura mater (literally meaning tough mother). Below the dura mater lies the arachnoid mater (literally spider-like mother). The innermost meningeal layer is a delicate membrane called the pia mater (literally tender mother). Unlike the other meningeal layers, the pia mater firmly adheres to the convoluted surface of the brain. Between the arachnoid mater and pia mater is the subarachnoid space. The subarachnoid space within this region is filled with cerebrospinal fluid (CSF). This watery fluid is produced by cells of the choroid plexus—areas in each ventricle of the brain that consist of cuboidal epithelial cells surrounding dense capillary beds. The CSF serves to deliver nutrients and remove waste from neural tissues.

Clinical Focus

Part 1

David is a 35-year-old carpenter from New Jersey. A year ago, he was diagnosed with Crohn's disease, a chronic inflammatory bowel disease that has no known cause. He has been taking a prescription corticosteroid to manage the condition, and the drug has been highly effective in keeping his symptoms at bay. However, David recently fell ill and decided to visit his primary care physician. His symptoms included a fever, a persistent cough, and shortness of breath. His physician ordered a chest X-ray, which revealed consolidation of the right lung. The doctor prescribed a course of levofloxacin and told David to come back in a week if he did not feel better.

- What type of drug is levofloxacin?
- What type of microbes would this drug be effective against?
- What type of infection is consistent with David’s symptoms?

Jump to the next Clinical Focus box.
Figure 26.2  The essential components of the human nervous system are shown in this illustration. The central nervous system (CNS) consists of the brain and spinal cord. It connects to the peripheral nervous system (PNS), a network of nerves that extends throughout the body.

Figure 26.3  The layers of tissue surrounding the human brain include three meningeal membranes: the dura mater, arachnoid mater, and pia mater. (credit: modification of work by National Institutes of Health)
The Blood-Brain Barrier

The tissues of the CNS have extra protection in that they are not exposed to blood or the immune system in the same way as other tissues. The blood vessels that supply the brain with nutrients and other chemical substances lie on top of the pia mater. The capillaries associated with these blood vessels in the brain are less permeable than those in other locations in the body. The capillary endothelial cells form tight junctions that control the transfer of blood components to the brain. In addition, cranial capillaries have far fewer fenestra (pore-like structures that are sealed by a membrane) and pinocytotic vesicles than other capillaries. As a result, materials in the circulatory system have a very limited ability to interact with the CNS directly. This phenomenon is referred to as the blood-brain barrier.

The blood-brain barrier protects the cerebrospinal fluid from contamination, and can be quite effective at excluding potential microbial pathogens. As a consequence of these defenses, there is no normal microbiota in the cerebrospinal fluid. The blood-brain barrier also inhibits the movement of many drugs into the brain, particularly compounds that are not lipid soluble. This has profound ramifications for treatments involving infections of the CNS, because it is difficult for drugs to cross the blood-brain barrier to interact with pathogens that cause infections.

The spinal cord also has protective structures similar to those surrounding the brain. Within the bones of the vertebrae are meninges of dura mater (sometimes called the dural sheath), arachnoid mater, pia mater, and a blood-spinal cord barrier that controls the transfer of blood components from blood vessels associated with the spinal cord.

To cause an infection in the CNS, pathogens must successfully breach the blood-brain barrier or blood-spinal cord barrier. Various pathogens employ different virulence factors and mechanisms to achieve this, but they can generally be grouped into four categories: intercellular (also called paracellular), transcellular, leukocyte facilitated, and nonhematogenous. Intercellular entry involves the use of microbial virulence factors, toxins, or inflammation-mediated processes to pass between the cells of the blood-brain barrier. In transcellular entry, the pathogen passes through the cells of the blood-brain barrier using virulence factors that allow it to adhere to and trigger uptake by vacuole- or receptor-mediated mechanisms. Leukocyte-facilitated entry is a Trojan-horse mechanism that occurs when a pathogen infects peripheral blood leukocytes to directly enter the CNS. Nonhematogenous entry allows pathogens to enter the brain without encountering the blood-brain barrier; it occurs when pathogens travel along either the olfactory or trigeminal cranial nerves that lead directly into the CNS.

Link to Learning

View this video (https://www.openstax.org/l/22bldbrbarr) about the blood-brain barrier

Check Your Understanding

- What is the primary function of the blood-brain barrier?

The Peripheral Nervous System

The PNS is formed of the nerves that connect organs, limbs, and other anatomic structures of the body to the brain and spinal cord. Unlike the brain and spinal cord, the PNS is not protected by bone, meninges, or a blood barrier, and, as a consequence, the nerves of the PNS are much more susceptible to injury and infection. Microbial damage to peripheral nerves can lead to tingling or numbness known as neuropathy. These symptoms can also be produced by trauma and noninfectious causes such as drugs or chronic diseases like diabetes.
The Cells of the Nervous System

Tissues of the PNS and CNS are formed of cells called **glial cells** (neuroglial cells) and **neurons** (nerve cells). Glial cells assist in the organization of neurons, provide a scaffold for some aspects of neuronal function, and aid in recovery from neural injury.

Neurons are specialized cells found throughout the nervous system that transmit signals through the nervous system using electrochemical processes. The basic structure of a neuron is shown in Figure 26.4. The cell body (or **soma**) is the metabolic center of the neuron and contains the nucleus and most of the cell’s organelles. The many finely branched extensions from the soma are called **dendrites**. The soma also produces an elongated extension, called the **axon**, which is responsible for the transmission of electrochemical signals through elaborate ion transport processes. Axons of some types of neurons can extend up to one meter in length in the human body. To facilitate electrochemical signal transmission, some neurons have a **myelin sheath** surrounding the axon. Myelin, formed from the cell membranes of glial cells like the Schwann cells in the PNS and oligodendrocytes in the CNS, surrounds and insulates the axon, significantly increasing the speed of electrochemical signal transmission along the axon. The end of an axon forms numerous branches that end in bulbs called synaptic terminals. Neurons form junctions with other cells, such as another neuron, with which they exchange signals. The junctions, which are actually gaps between neurons, are referred to as **synapses**. At each synapse, there is a presynaptic neuron and a postsynaptic neuron (or other cell). The synaptic terminals of the axon of the presynaptic terminal form the synapse with the dendrites, soma, or sometimes the axon of the postsynaptic neuron, or a part of another type of cell such as a muscle cell. The synaptic terminals contain vesicles filled with chemicals called **neurotransmitters**. When the electrochemical signal moving down the axon reaches the synapse, the vesicles fuse with the membrane, and neurotransmitters are released, which diffuse across the synapse and bind to receptors on the membrane of the postsynaptic cell, potentially initiating a response in that cell. That response in the postsynaptic cell might include further propagation of an electrochemical signal to transmit information or contraction of a muscle fiber.

![Figure 26.4](image-url) (a) A myelinated neuron is associated with oligodendrocytes. Oligodendrocytes are a type of glial cell that forms the myelin sheath in the CNS that insulates the axon so that electrochemical nerve impulses are transferred more efficiently. (b) A synapse consists of the axonal end of the presynaptic neuron (top) that releases neurotransmitters that cross the synaptic space (or cleft) and bind to receptors on dendrites of the postsynaptic neuron (bottom).
Meningitis and Encephalitis

Although the skull provides the brain with an excellent defense, it can also become problematic during infections. Any swelling of the brain or meninges that results from inflammation can cause intracranial pressure, leading to severe damage of the brain tissues, which have limited space to expand within the inflexible bones of the skull. The term meningitis is used to describe an inflammation of the meninges. Typical symptoms can include severe headache, fever, photophobia (increased sensitivity to light), stiff neck, convulsions, and confusion. An inflammation of brain tissue is called encephalitis, and patients exhibit signs and symptoms similar to those of meningitis in addition to lethargy, seizures, and personality changes. When inflammation affects both the meninges and the brain tissue, the condition is called meningoencephalitis. All three forms of inflammation are serious and can lead to blindness, deafness, coma, and death.

Meningitis and encephalitis can be caused by many different types of microbial pathogens. However, these conditions can also arise from noninfectious causes such as head trauma, some cancers, and certain drugs that trigger inflammation. To determine whether the inflammation is caused by a pathogen, a lumbar puncture is performed to obtain a sample of CSF. If the CSF contains increased levels of white blood cells and abnormal glucose and protein levels, this indicates that the inflammation is a response to an infection.

Guillain-Barré Syndrome

Guillain-Barré syndrome (GBS) is a rare condition that can be preceded by a viral or bacterial infection that results in an autoimmune reaction against myelinated nerve cells. The destruction of the myelin sheath around these neurons results in a loss of sensation and function. The first symptoms of this condition are tingling and weakness in the affected tissues. The symptoms intensify over a period of several weeks and can culminate in complete paralysis. Severe cases can be life-threatening. Infections by several different microbial pathogens, including Campylobacter jejuni (the most common risk factor), cytomegalovirus, Epstein-Barr virus, varicella-zoster virus, Mycoplasma pneumoniae,[1] and Zika virus[2] have been identified as triggers for GBS. Anti-myelin antibodies from patients with GBS have been demonstrated to also recognize C. jejuni. It is possible that cross-reactive antibodies, antibodies that react with similar antigenic sites on different proteins, might be formed during an infection and may lead to this autoimmune response.

GBS is solely identified by the appearance of clinical symptoms. There are no other diagnostic tests available. Fortunately, most cases spontaneously resolve within a few months with few permanent effects, as there is no available vaccine. GBS can be treated by plasmapheresis. In this procedure, the patient's plasma is filtered from their blood, removing autoantibodies.
26.2 Bacterial Diseases of the Nervous System

Learning Objectives

• Identify the most common bacteria that can cause infections of the nervous system
• Compare the major characteristics of specific bacterial diseases affecting the nervous system

Bacterial infections that affect the nervous system are serious and can be life-threatening. Fortunately, there are only a few bacterial species commonly associated with neurological infections.

Bacterial Meningitis

Bacterial meningitis is one of the most serious forms of meningitis. Bacteria that cause meningitis often gain access to the CNS through the bloodstream after trauma or as a result of the action of bacterial toxins. Bacteria may also spread from structures in the upper respiratory tract, such as the oropharynx, nasopharynx, sinuses, and middle ear. Patients with head wounds or cochlear implants (an electronic device placed in the inner ear) are also at risk for developing meningitis.

Many of the bacteria that can cause meningitis are commonly found in healthy people. The most common causes of non-neonatal bacterial meningitis are Neisseria meningitidis, Streptococcus pneumoniae, and Haemophilus influenzae. All three of these bacterial pathogens are spread from person to person by respiratory secretions. Each can colonize and cross through the mucous membranes of the oropharynx and nasopharynx, and enter the blood. Once in the blood, these pathogens can disseminate throughout the body and are capable of both establishing an infection and triggering inflammation in any body site, including the meninges (Figure 26.5). Without appropriate systemic antibacterial therapy, the case-fatality rate can be as high as 70%, and 20% of those survivors may be left with irreversible nerve damage or tissue destruction, resulting in hearing loss, neurologic disability, or loss of a limb. Mortality rates are much lower (as low as 15%) in populations where appropriate therapeutic drugs and preventive vaccines are available.[3]

Figure 26.5 (a) A normal human brain removed during an autopsy. (b) The brain of a patient who died from bacterial meningitis. Note the pus under the dura mater (being retracted by the forceps) and the red hemorrhagic foci on the meninges. (credit b: modification of work by the Centers for Disease Control and Prevention)

A variety of other bacteria, including *Listeria monocytogenes* and *Escherichia coli*, are also capable of causing meningitis. These bacteria cause infections of the arachnoid mater and CSF after spreading through the circulation in blood or by spreading from an infection of the sinuses or nasopharynx. *Streptococcus agalactiae*, commonly found in the microbiota of the vagina and gastrointestinal tract, can also cause bacterial meningitis in newborns after transmission from the mother either before or during birth.

The profound inflammation caused by these microbes can result in early symptoms that include severe headache, fever, confusion, nausea, vomiting, photophobia, and stiff neck. Systemic inflammatory responses associated with some types of bacterial meningitis can lead to hemorrhaging and purpuric lesions on skin, followed by even more severe conditions that include shock, convulsions, coma, and death—in some cases, in the span of just a few hours.

Diagnosis of bacterial meningitis is best confirmed by analysis of CSF obtained by a lumbar puncture. Abnormal levels of polymorphonuclear neutrophils (PMNs) (> 10 PMNs/mm$^3$), glucose (< 45 mg/dL), and protein (> 45 mg/dL) in the CSF are suggestive of bacterial meningitis.$^{[4]}$ Characteristics of specific forms of bacterial meningitis are detailed in the subsections that follow.

### Meningococcal Meningitis

*Meningococcal meningitis* is a serious infection caused by the gram-negative coccus *N. meningitidis*. In some cases, death can occur within a few hours of the onset of symptoms. Nonfatal cases can result in irreversible nerve damage, resulting in hearing loss and brain damage, or amputation of extremities because of tissue necrosis.

Meningococcal meningitis can infect people of any age, but its prevalence is highest among infants, adolescents, and young adults.$^{[5]}$ Meningococcal meningitis was once the most common cause of meningitis epidemics in human populations. This is still the case in a swath of sub-Saharan Africa known as the meningitis belt, but meningococcal meningitis epidemics have become rare in most other regions, thanks to meningococcal vaccines. However, outbreaks can still occur in communities, schools, colleges, prisons, and other populations where people are in close direct contact.

*N. meningitidis* has a high affinity for mucosal membranes in the oropharynx and nasopharynx. Contact with respiratory secretions containing *N. meningitidis* is an effective mode of transmission. The pathogenicity of *N. meningitidis* is enhanced by virulence factors that contribute to the rapid progression of the disease. These include lipoooligosaccharide (LOS) endotoxin, type IV pili for attachment to host tissues, and polysaccharide capsules that help the cells avoid phagocytosis and complement-mediated killing. Additional virulence factors include IgA protease (which breaks down IgA antibodies), the invasion factors Opa, Opc, and porin (which facilitate transcellular entry through the blood-brain barrier), iron-uptake factors (which strip heme units from hemoglobin in host cells and use them for growth), and stress proteins that protect bacteria from reactive oxygen molecules.

A unique sign of meningococcal meningitis is the formation of a petechial rash on the skin or mucous membranes, characterized by tiny, red, flat, hemorrhagic lesions. This rash, which appears soon after disease onset, is a response to LOS endotoxin and adherence virulence factors that disrupt the endothelial cells of capillaries and small veins in the skin. The blood vessel disruption triggers the formation of tiny blood clots, causing blood to leak into the surrounding tissue. As the infection progresses, the levels of virulence factors increase, and the hemorrhagic lesions can increase in size as blood continues to leak into tissues. Lesions larger than 1.0 cm usually occur in patients developing shock, as virulence factors cause increased hemorrhage and clot formation. Sepsis, as a result of systemic damage from meningococcal virulence factors, can lead to rapid multiple organ failure, shock, disseminated intravascular coagulation, and death.

Because meningococcal meningitis progresses so rapidly, a greater variety of clinical specimens are required for the timely detection of *N. meningitidis*. Required specimens can include blood, CSF, naso- and oropharyngeal swabs, urethral and endocervical swabs, petechial aspirates, and biopsies. Safety protocols for handling and transport of

specimens suspected of containing *N. meningitidis* should always be followed, since cases of fatal meningococcal disease have occurred in healthcare workers exposed to droplets or aerosols from patient specimens. Prompt presumptive diagnosis of meningococcal meningitis can occur when CSF is directly evaluated by Gram stain, revealing extra- and intracellular gram-negative diplococci with a distinctive coffee-bean microscopic morphology associated with PMNs (Figure 26.6). Identification can also be made directly from CSF using latex agglutination and immunochromatographic rapid diagnostic tests specific for *N. meningitidis*. Species identification can also be performed using DNA sequence-based typing schemes for hypervariable outer membrane proteins of *N. meningitidis*, which has replaced sero(sub)typing.

Meningococcal infections can be treated with antibiotic therapy, and third-generation cephalosporins are most often employed. However, because outcomes can be negative even with treatment, preventive vaccination is the best form of treatment. In 2010, countries in Africa’s meningitis belt began using a new serogroup A meningococcal conjugate vaccine. This program has dramatically reduced the number of cases of meningococcal meningitis by conferring individual and herd immunity.

Twelve different capsular serotypes of *N. meningitidis* are known to exist. Serotypes A, B, C, W, X, and Y are the most prevalent worldwide. The CDC recommends that children between 11–12 years of age be vaccinated with a single dose of a quadrivalent vaccine that protects against serotypes A, C, W, and Y, with a booster at age 16. An additional booster or injections of serogroup B meningococcal vaccine may be given to individuals in high-risk settings (such as epidemic outbreaks on college campuses).

![Figure 26.6](image) *N. meningitidis* (arrows) associated with neutrophils (the larger stained cells) in a gram-stained CSF sample. (credit: modification of work by the Centers for Disease Control and Prevention)

### Micro Connections

**Meningitis on Campus**

College students living in dorms or communal housing are at increased risk for contracting epidemic meningitis. From 2011 to 2015, there have been at least nine meningococcal outbreaks on college campuses in the United States. These incidents involved a total of 43 students (of whom four died) in spite of rapid diagnosis and aggressive antimicrobial treatment, several of the survivors suffered from amputations or serious neurological problems.

Prophylactic vaccination of first-year college students living in dorms is recommended by the CDC, and insurance companies now cover meningococcal vaccination for students in college dorms. Some colleges have mandated vaccination with meningococcal conjugate vaccine for certain students entering college (Figure 26.7).

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Pneumococcal Meningitis

Pneumococcal meningitis is caused by the encapsulated gram-positive bacterium *S. pneumoniae* (pneumococcus, also called strep pneumo). This organism is commonly found in the microbiota of the pharynx of 30–70% of young children, depending on the sampling method, while *S. pneumoniae* can be found in fewer than 5% of healthy adults. Although it is often present without disease symptoms, this microbe can cross the blood-brain barrier in susceptible individuals. In some cases, it may also result in septicemia. Since the introduction of the Hib vaccine, *S. pneumoniae* has become the leading cause of meningitis in humans aged 2 months through adulthood.

*S. pneumoniae* can be identified in CSF samples using gram-stained specimens, latex agglutination, and immunochromatographic RDT specific for *S. pneumoniae*. In gram-stained samples, *S. pneumoniae* appears as gram-positive, lancet-shaped diplococci (Figure 26.8). Identification of *S. pneumoniae* can also be achieved using cultures of CSF and blood, and at least 93 distinct serotypes can be identified based on the quellung reaction to unique capsular polysaccharides. PCR and RT-PCR assays are also available to confirm identification.

Major virulence factors produced by *S. pneumoniae* include PI-1 pilin for adherence to host cells (pneumococcal adherence) and virulence factor B (PavB) for attachment to cells of the respiratory tract; choline-binding proteins (cbpA) that bind to epithelial cells and interfere with immune factors IgA and C3; and the cytoplasmic bacterial toxin pneumolysin that triggers an inflammatory response.

With the emergence of drug-resistant strains of *S. pneumoniae*, pneumococcal meningitis is typically treated with broad-spectrum antibiotics, such as levofloxacin, cefotaxime, penicillin, or other β-lactam antibiotics. The two available pneumococcal vaccines are described in *Bacterial Infections of the Respiratory Tract*.

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Haemophilus influenzae Type b

Meningitis due to H. influenzae serotype b (Hib), an encapsulated pleomorphic gram-negative coccobacilli, is now uncommon in most countries, because of the use of the effective Hib vaccine. Without the use of the Hib vaccine, H. influenzae can be the primary cause of meningitis in children 2 months thru 5 years of age. H. influenzae can be found in the throats of healthy individuals, including infants and young children. By five years of age, most children have developed immunity to this microbe. Infants older than 2 months of age, however, do not produce a sufficient protective antibody response and are susceptible to serious disease. The intracranial pressure caused by this infection leads to a 5% mortality rate and 20% incidence of deafness or brain damage in survivors.⁸

H. influenzae produces at least 16 different virulence factors, including LOS, which triggers inflammation, and Haemophilus adhesion and penetration factor (Hap), which aids in attachment and invasion into respiratory epithelial cells. The bacterium also has a polysaccharide capsule that helps it avoid phagocytosis, as well as factors such as IgA1 protease and P2 protein that allow it to evade antibodies secreted from mucous membranes. In addition, factors such as hemoglobin-binding protein (Hgp) and transferrin-binding protein (Tbp) acquire iron from hemoglobin and transferrin, respectively, for bacterial growth.

Preliminary diagnosis of H. influenzae infections can be made by direct PCR and a smear of CSF. Stained smears will reveal intracellular and extracellular PMNs with small, pleomorphic, gram-negative coccobacilli or filamentous forms that are characteristic of H. influenzae. Initial confirmation of this genus can be based on its fastidious growth on chocolate agar. Identification is confirmed with requirements for exogenous biochemical growth cofactors NAD and heme (by MALDI-TOF), latex agglutination, and RT-PCR.

Meningitis caused by H. influenzae is usually treated with doxycycline, fluoroquinolones, second- and third-generation cephalosporins, and carbapenems. The best means of preventing H. influenza infection is with the use of the Hib polysaccharide conjugate vaccine. It is recommended that all children receive this vaccine at 2, 4, and 6 months of age, with a final booster dose at 12 to 15 months of age.⁹

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Neonatal Meningitis

*S. agalactiae*, Group B streptococcus (GBS), is an encapsulated gram-positive bacterium that is the most common cause of neonatal meningitis, a term that refers to meningitis occurring in babies up to 3 months of age.\(^\text{10}\) *S. agalactiae* can also cause meningitis in people of all ages and can be found in the urogenital and gastrointestinal microbiota of about 10–30% of humans.

Neonatal infection occurs as either early onset or late-onset disease. Early onset disease is defined as occurring in infants up to 7 days old. The infant initially becomes infected by *S. agalactiae* during childbirth, when the bacteria may be transferred from the mother’s vagina. Incidence of early onset neonatal meningitis can be greatly reduced by giving intravenous antibiotics to the mother during labor.

Late-onset neonatal meningitis occurs in infants between 1 week and 3 months of age. Infants born to mothers with *S. agalactiae* in the urogenital tract have a higher risk of late-onset meningitis, but late-onset infections can be transmitted from sources other than the mother; often, the source of infection is unknown. Infants who are born prematurely (before 37 weeks of pregnancy) or to mothers who develop a fever also have a greater risk of contracting late-onset neonatal meningitis.

Signs and symptoms of early onset disease include temperature instability, apnea (cessation of breathing), bradycardia (slow heart rate), hypotension, difficulty feeding, irritability, and limpness. When asleep, the baby may be difficult to wake up. Symptoms of late-onset disease are more likely to include seizures, bulging fontanel (soft spot), stiff neck, hemiparesis (weakness on one side of the body), and opisthotonos (rigid body with arched back and head thrown backward).

*S. agalactiae* produces at least 12 virulence factors that include FbsA that attaches to host cell surface proteins, PI-1 pili that promotes the invasion of human endothelial cells, a polysaccharide capsule that prevents the activation of the alternative complement pathway and inhibits phagocytosis, and the toxin CAMP factor, which forms pores in host cell membranes and binds to IgG and IgM antibodies.

Diagnosis of neonatal meningitis is often, but not uniformly, confirmed by positive results from cultures of CSF or blood. Tests include routine culture, antigen detection by enzyme immunoassay, serotyping of different capsule types, PCR, and RT-PCR. It is typically treated with β-lactam antibiotics such as intravenous penicillin or ampicillin plus gentamicin. Even with treatment, roughly 10% mortality is seen in infected neonates.\(^\text{11}\)

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### Check Your Understanding

- Which groups are most vulnerable to each of the bacterial meningitis diseases?
- For which of the bacterial meningitis diseases are there vaccines presently available?
- Which organism can cause epidemic meningitis?

### Clostridium-Associated Diseases

Species in the genus *Clostridium* are gram-positive, endospore-forming rods that are obligate anaerobes. Endospores of *Clostridium* spp. are widespread in nature, commonly found in soil, water, feces, sewage, and marine sediments. *Clostridium* spp. produce more types of protein exotoxins than any other bacterial genus, including two exotoxins.
with protease activity that are the most potent known biological toxins: botulinum neurotoxin (BoNT) and tetanus neurotoxin (TeNT). These two toxins have lethal doses of 0.2–10 ng per kg body weight.

BoNT can be produced by unique strains of *C. butyricum*, and *C. baratii*; however, it is primarily associated with *C. botulinum* and the condition of botulism. TeNT, which causes tetanus, is only produced by *C. tetani*. These powerful neural exotoxins are the primary virulence factors for these pathogens. The mode of action for these toxins was described in *Virulence Factors of Bacterial and Viral Pathogens* and illustrated in Figure 15.16.

Diagnosis of tetanus or botulism typically involves bioassays that detect the presence of BoNT and TeNT in fecal specimens, blood (serum), or suspect foods. In addition, both *C. botulinum* and *C. tetani* can be isolated and cultured using commercially available media for anaerobes. ELISA and RT-PCR tests are also available.

**Tetanus**

*Tetanus* is a noncommunicable disease characterized by uncontrollable muscle spasms (contractions) caused by the action of TeNT. It generally occurs when *C. tetani* infects a wound and produces TeNT, which rapidly binds to neural tissue, resulting in an intoxication (poisoning) of neurons. Depending on the site and extent of infection, cases of tetanus can be described as localized, cephalic, or generalized. Generalized tetanus that occurs in a newborn is called neonatal tetanus.

Localized tetanus occurs when TeNT only affects the muscle groups close to the injury site. There is no CNS involvement, and the symptoms are usually mild, with localized muscle spasms caused by a dysfunction in the surrounding neurons. Individuals with partial immunity—especially previously vaccinated individuals who neglect to get the recommended booster shots—are most likely to develop localized tetanus as a result of *C. tetani* infecting a puncture wound.

Cephalic tetanus is a rare, localized form of tetanus generally associated with wounds on the head or face. In rare cases, it has occurred in cases of otitis media (middle ear infection). Cephalic tetanus often results in patients seeing double images, because of the spasms affecting the muscles that control eye movement.

Both localized and cephalic tetanus may progress to generalized tetanus—a much more serious condition—if TeNT is able to spread further into body tissues. In generalized tetanus, TeNT enters neurons of the PNS. From there, TeNT travels from the site of the wound, usually on an extremity of the body, retrograde (back up) to inhibitory neurons in the CNS. There, it prevents the release of gamma aminobutyric acid (GABA), the neurotransmitter responsible for muscle relaxation. The resulting muscle spasms often first occur in the jaw muscles, leading to the characteristic symptom of lockjaw (inability to open the mouth). As the toxin progressively continues to block neurotransmitter release, other muscles become involved, resulting in uncontrollable, sudden muscle spasms that are powerful enough to cause tendons to rupture and bones to fracture. Spasms in the muscles in the neck, back, and legs may cause the body to form a rigid, stiff arch, a posture called opisthotonos (*Figure 26.9*). Spasms in the larynx, diaphragm, and muscles of the chest restrict the patient’s ability to swallow and breathe, eventually leading to death by asphyxiation (insufficient supply of oxygen).

**Neonatal tetanus** typically occurs when the stump of the umbilical cord is contaminated with spores of *C. tetani* after delivery. Although this condition is rare in the United States, neonatal tetanus is a major cause of infant mortality in countries that lack maternal immunization for tetanus and where birth often occurs in unsanitary conditions. At the end of the first week of life, infected infants become irritable, feed poorly, and develop rigidity with spasms. Neonatal tetanus has a very poor prognosis with a mortality rate of 70%–100%.[12]

Treatment for patients with tetanus includes assisted breathing through the use of a ventilator, wound debridement, fluid balance, and antibiotic therapy with metronidazole or penicillin to halt the growth of *C. tetani*. In addition, patients are treated with TeNT antitoxin, preferably in the form of human immunoglobulin to neutralize nonfixed toxin and benzodiazepines to enhance the effect of GABA for muscle relaxation and anxiety.

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A tetanus toxoid (TT) vaccine is available for protection and prevention of tetanus. It is the T component of vaccines such as DTaP, Tdap, and Td. The CDC recommends children receive doses of the DTaP vaccine at 2, 4, 6, and 15–18 months of age and another at 4–6 years of age. One dose of Td is recommended for adolescents and adults as a TT booster every 10 years.\[^{13}\]

![Figure 26.9](https://example.com/figure26.9.jpg) A tetanus patient exhibiting the rigid body posture known as opisthotonos. (credit: Centers for Disease Control and Prevention)

**Botulism**

Botulism is a rare but frequently fatal illness caused by intoxication by BoNT. It can occur either as the result of an infection by *C. botulinum*, in which case the bacteria produce BoNT *in vivo*, or as the result of a direct introduction of BoNT into tissues.

Infection and production of BoNT *in vivo* can result in wound botulism, infant botulism, and adult intestinal toxemia. Wound botulism typically occurs when *C. botulinum* is introduced directly into a wound after a traumatic injury, deep puncture wound, or injection site. Infant botulism, which occurs in infants younger than 1 year of age, and adult intestinal toxemia, which occurs in immunocompromised adults, results from ingesting *C. botulinum* endospores in food. The endospores germinate in the body, resulting in the production of BoNT in the intestinal tract.

Intoxications occur when BoNT is produced outside the body and then introduced directly into the body through food (foodborne botulism), air (inhalation botulism), or a clinical procedure (iatrogenic botulism). Foodborne botulism, the most common of these forms, occurs when BoNT is produced in contaminated food and then ingested along with the food (recall **Case in Point: A Streak of Bad Potluck**). Inhalation botulism is rare because BoNT is unstable as an aerosol and does not occur in nature; however, it can be produced in the laboratory and was used (unsuccessfully) as a bioweapon by terrorists in Japan in the 1990s. A few cases of accidental inhalation botulism have also occurred. Iatrogenic botulism is also rare; it is associated with injections of BoNT used for cosmetic purposes (see **Micro Connections: Medicinal Uses of Botulinum Toxin**).

When BoNT enters the bloodstream in the gastrointestinal tract, wound, or lungs, it is transferred to the neuromuscular junctions of motor neurons where it binds irreversibly to presynaptic membranes and prevents the release of acetylcholine from the presynaptic terminal of motor neurons into the neuromuscular junction. The consequence of preventing acetylcholine release is the loss of muscle activity, leading to muscle relaxation and eventually paralysis.

If BoNT is absorbed through the gastrointestinal tract, early symptoms of botulism include blurred vision, drooping eyelids, difficulty swallowing, abdominal cramps, nausea, vomiting, constipation, or possibly diarrhea. This is

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followed by progressive flaccid paralysis, a gradual weakening and loss of control over the muscles. A patient’s experience can be particularly terrifying, because hearing remains normal, consciousness is not lost, and he or she is fully aware of the progression of his or her condition. In infants, notable signs of botulism include weak cry, decreased ability to suckle, and hypotonia (limpness of head or body). Eventually, botulism ends in death from respiratory failure caused by the progressive paralysis of the muscles of the upper airway, diaphragm, and chest.

Botulism is treated with an antitoxin specific for BoNT. If administered in time, the antitoxin stops the progression of paralysis but does not reverse it. Once the antitoxin has been administered, the patient will slowly regain neurological function, but this may take several weeks or months, depending on the severity of the case. During recovery, patients generally must remain hospitalized and receive breathing assistance through a ventilator.

**Check Your Understanding**

- How frequently should the tetanus vaccination be updated in adults?
- What are the most common causes of botulism?
- Why is botulism not treated with an antibiotic?

**Micro Connections**

**Medicinal Uses of Botulinum Toxin**

Although it is the most toxic biological material known to man, botulinum toxin is often intentionally injected into people to treat other conditions. Type A botulinum toxin is used cosmetically to reduce wrinkles. The injection of minute quantities of this toxin into the face causes the relaxation of facial muscles, thereby giving the skin a smoother appearance. Eyelid twitching and crossed eyes can also be treated with botulinum toxin injections. Other uses of this toxin include the treatment of hyperhidrosis (excessive sweating). In fact, botulinum toxin can be used to moderate the effects of several other apparently nonmicrobial diseases involving inappropriate nerve function. Such diseases include cerebral palsy, multiple sclerosis, and Parkinson’s disease. Each of these diseases is characterized by a loss of control over muscle contractions; treatment with botulinum toxin serves to relax contracted muscles.

**Listeriosis**

*Listeria monocytogenes* is a nonencapsulated, nonsporulating, gram-positive rod and a foodborne pathogen that causes *listeriosis*. At-risk groups include pregnant women, neonates, the elderly, and the immunocompromised (recall the Clinical Focus case studies in *Microbial Growth* and *Microbial Mechanisms of Pathogenicity*). Listeriosis leads to meningitis in about 20% of cases, particularly neonates and patients over the age of 60. The CDC identifies listeriosis as the third leading cause of death due to foodborne illness, with overall mortality rates reaching 16%. In pregnant women, listeriosis can cause also cause spontaneous abortion in pregnant women because of the pathogen’s unique ability to cross the placenta.

*L. monocytogenes* is generally introduced into food items by contamination with soil or animal manure used as fertilizer. Foods commonly associated with listeriosis include fresh fruits and vegetables, frozen vegetables, processed

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meats, soft cheeses, and raw milk. Unlike most other foodborne pathogens, *Listeria* is able to grow at temperatures between 0 °C and 50 °C, and can therefore continue to grow, even in refrigerated foods.

Ingestion of contaminated food leads initially to infection of the gastrointestinal tract. However, *L. monocytogenes* produces several unique virulence factors that allow it to cross the intestinal barrier and spread to other body systems. Surface proteins called internalins (InlA and InlB) help *L. monocytogenes* invade nonphagocytic cells and tissues, penetrating the intestinal wall and becoming disseminating through the circulatory and lymphatic systems. Internalins also enable *L. monocytogenes* to breach other important barriers, including the blood-brain barrier and the placenta. Within tissues, *L. monocytogenes* uses other proteins called listeriolysin O and ActA to facilitate intercellular movement, allowing the infection to spread from cell to cell (Figure 26.10).

*L. monocytogenes* is usually identified by cultivation of samples from a normally sterile site (e.g., blood or CSF). Recovery of viable organisms can be enhanced using cold enrichment by incubating samples in a broth at 4 °C for a week or more. Distinguishing types and subtypes of *L. monocytogenes*—an important step for diagnosis and epidemiology—is typically done using pulsed-field gel electrophoresis. Identification can also be achieved using chemiluminescence DNA probe assays and MALDI-TOF.

Treatment for listeriosis involves antibiotic therapy, most commonly with ampicillin and gentamicin. There is no vaccine available.

**Figure 26.10** (a) An electron micrograph of *Listeria monocytogenes* infecting a host cell. (b) *Listeria* is able to use host cell components to cause infection. For example, phagocytosis allows it to enter host cells, and the host’s cytoskeleton provides the materials to help the pathogen move to other cells. (credit a: modification of work by the Centers for Disease Control and Prevention; credit b: modification of work by Keith Ireton)

- How does *Listeria* enter the nervous system?

**Hansen’s Disease (Leprosy)**

Hansen’s disease (also known as leprosy) is caused by a long, thin, filamentous rod-shaped bacterium *Mycobacterium leprae*, an obligate intracellular pathogen. *M. leprae* is classified as gram-positive bacteria, but it is best visualized microscopically with an acid-fast stain and is generally referred to as an acid-fast bacterium. Hansen’s disease affects the PNS, leading to permanent damage and loss of appendages or other body parts.

Hansen’s disease is communicable but not highly contagious; approximately 95% of the human population cannot be easily infected because they have a natural immunity to *M. leprae*. Person-to-person transmission occurs by inhalation into nasal mucosa or prolonged and repeated contact with infected skin. Armadillos, one of only five mammals susceptible to Hansen’s disease, have also been implicated in transmission of some cases.\(^{[16]}\)

In the human body, *M. leprae* grows best at the cooler temperatures found in peripheral tissues like the nose, toes, fingers, and ears. Some of the virulence factors that contribute to *M. leprae*’s pathogenicity are located on the capsule and cell wall of the bacterium. These virulence factors enable it to bind to and invade Schwann cells, resulting in progressive demyelination that gradually destroys neurons of the PNS. The loss of neuronal function leads to hypoesthesia (numbness) in infected lesions. *M. leprae* is readily phagocytized by macrophages but is able to survive within macrophages in part by neutralizing reactive oxygen species produced in the oxidative burst of the phagolysosome. Like *L. monocytogenes*, *M. leprae* also can move directly between macrophages to avoid clearance by immune factors.

The extent of the disease is related to the immune response of the patient. Initial symptoms may not appear for as long as 2 to 5 years after infection. These often begin with small, blanched, numb areas of the skin. In most individuals, these will resolve spontaneously, but some cases may progress to a more serious form of the disease. Tuberculoid (paucibacillary) Hansen’s disease is marked by the presence of relatively few (three or less) flat, blanched skin lesions with small nodules at the edges and few bacteria present in the lesion. Although these lesions can persist for years or decades, the bacteria are held in check by an effective immune response including cell-mediated cytotoxicity. Individuals who are unable to contain the infection may later develop lepromatous (multibacillary) Hansen’s disease. This is a progressive form of the disease characterized by nodules filled with acid-fast bacilli and macrophages. Impaired function of infected Schwann cells leads to peripheral nerve damage, resulting in sensory loss that leads to ulcers, deformities, and fractures. Damage to the ulnar nerve (in the wrist) by *M. leprae* is one of the most common causes of crippling of the hand. In some cases, chronic tissue damage can ultimately lead to loss of fingers or toes. When mucosal tissues are also involved, disfiguring lesions of the nose and face can also occur (Figure 26.11).

Hansen’s disease is diagnosed on the basis of clinical signs and symptoms of the disease, and confirmed by the presence of acid-fast bacilli on skin smears or in skin biopsy specimens (Figure 26.11). *M. leprae* does not grow *in vitro* on any known laboratory media, but it can be identified by culturing *in vivo* in the footpads of laboratory mice or armadillos. Where needed, PCR and genotyping of *M. leprae* DNA in infected human tissue may be performed for diagnosis and epidemiology.

Hansen’s disease responds well to treatment and, if diagnosed and treated early, does not cause disability. In the United States, most patients with Hansen’s disease are treated in ambulatory care clinics in major cities by the National Hansen’s Disease program, the only institution in the United States exclusively devoted to Hansen’s disease. Since 1995, WHO has made multidrug therapy for Hansen’s disease available free of charge to all patients worldwide. As a result, global prevalence of Hansen’s disease has declined from about 5.2 million cases in 1985 to roughly 176,000 in 2014.\(^{[17]}\) Multidrug therapy consists of dapsone and rifampicin for all patients and a third drug, clofazimine, for patients with multibacillary disease.

Currently, there is no universally accepted vaccine for Hansen’s disease. India and Brazil use a tuberculosis vaccine against Hansen’s disease because both diseases are caused by species of *Mycobacterium*. The effectiveness of this method is questionable, however, since it appears that the vaccine works in some populations but not in others.

Figure 26.11  (a) The nose of a patient with Hansen's disease. Note the lepromatous/multibacillary lesions around the nostril. (b) Hansen's disease is caused by *Mycobacterium leprae*, a gram-positive bacillus. (credit a, b: modifications of work by the Centers for Disease Control and Prevention)

**Check Your Understanding**

- What prevents the progression from tuberculoid to lepromatous leprosy?
- Why does Hansen’s disease typically affect the nerves of the extremities?

**Eye on Ethics**

**Leper Colonies**

Disfiguring, deadly diseases like leprosy have historically been stigmatized in many cultures. Before leprosy was understood, victims were often isolated in leper colonies, a practice mentioned frequently in ancient texts, including the Bible. But leper colonies are not just an artifact of the ancient world. In Hawaii, a leper colony established in the late nineteenth century persisted until the mid-twentieth century, its residents forced to live in deplorable conditions.[18] Although leprosy is a communicable disease, it is not considered contagious (easily communicable), and it certainly does not pose enough of a threat to justify the permanent isolation of its victims. Today, we reserve the practices of isolation and quarantine to patients with more dangerous diseases, such as Ebola or multiple-drug-resistant bacteria like *Mycobacterium tuberculosis* and *Staphylococcus aureus*. The ethical argument for this practice is that isolating infected patients is necessary to prevent the transmission and spread of highly contagious diseases—even when it goes against the wishes of the patient.

Of course, it is much easier to justify the practice of temporary, clinical quarantining than permanent social segregation, as occurred in leper colonies. In the 1980s, there were calls by some groups to establish camps for people infected with AIDS. Although this idea was never actually implemented, it begs the question—where do we draw the line? Are permanent isolation camps or colonies ever medically or socially justifiable? Suppose there were an outbreak of a fatal, contagious disease for which there is no treatment. Would it be justifiable to impose social isolation on those afflicted with the disease? How would we balance the rights of the infected with the risk they pose to others? To what extent should society expect individuals to put their own health at risk for the sake of treating others humanely?
Bacterial Infections of the Nervous System

Despite the formidable defenses protecting the nervous system, a number of bacterial pathogens are known to cause serious infections of the CNS or PNS. Unfortunately, these infections are often serious and life threatening. Figure 26.12 summarizes some important infections of the nervous system.
<table>
<thead>
<tr>
<th>Disease</th>
<th>Pathogen</th>
<th>Signs and Symptoms</th>
<th>Transmission</th>
<th>Antimicrobial Drugs</th>
<th>Vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Botulism</td>
<td><em>Clostridium botulinum</em></td>
<td>Blurred vision, drooping eyelids, difficulty swallowing and breathing, nausea, vomiting, often fatal</td>
<td>Ingestion of preformed toxin in food, ingestion of endospores in food by infants or immunocompromised adults, bacterium introduced via wound or injection</td>
<td>Antitoxin; penicillin (for wound botulism)</td>
<td>None</td>
</tr>
<tr>
<td>Hansen's disease (leprosy)</td>
<td><em>Mycobacterium leprae</em></td>
<td>Hypopigmented skin, skin lesions, and nodules, loss of peripheral nerve function, loss of fingers, toes, and extremities</td>
<td>Inhalation, possible transmissible from armadillos to humans</td>
<td>Dapsone, rifampin, clofazimin</td>
<td>None</td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em> type b meningitis</td>
<td><em>Haemophilus influenzae</em></td>
<td>Nausea, vomiting, photophobia, stiff neck, confusion</td>
<td>Direct contact, inhalation of aerosols</td>
<td>Doxycycline, fluoroquinolones, second- and third-generation cephalosporins, and carbapenems</td>
<td>Hib vaccine</td>
</tr>
<tr>
<td>Listeriosis</td>
<td><em>Listeria monocytogenes</em></td>
<td>Initial flu-like symptoms, sepsis and potentially fatal meningitis in susceptible individuals, miscarriage in pregnant women</td>
<td>Bacterium ingested with contaminated food or water</td>
<td>Ampicillin, gentamicin</td>
<td>None</td>
</tr>
<tr>
<td>Meningococcal meningitis</td>
<td><em>Neisseria meningitidis</em></td>
<td>Nausea, vomiting, photophobia, stiff neck, confusion; often fatal</td>
<td>Direct contact</td>
<td>Cephalosporins or penicillins</td>
<td>Meningococcal conjugate</td>
</tr>
<tr>
<td>Neonatal meningitis</td>
<td><em>Streptococcus agalactiae</em></td>
<td>Temperature instability, apnea, bradycardia, hypotension, feeding difficulty, irritability, limping, seizures, bulging fontanel, stiff neck, opisthotonos, hemiparesis, often fatal</td>
<td>Direct contact in birth canal</td>
<td>Ampicillin plus gentamicin, cefotaxime, or both</td>
<td>None</td>
</tr>
<tr>
<td>Pneumococcal meningitis</td>
<td><em>Streptococcus pneumoniae</em></td>
<td>Nausea, vomiting, photophobia, stiff neck, confusion, often fatal</td>
<td>Direct contact, aerosols</td>
<td>Cephalosporins, penicillin</td>
<td>Pneumococcal vaccines</td>
</tr>
<tr>
<td>Tetanus</td>
<td><em>Clostridium tetani</em></td>
<td>Progressive spastic paralysis starting with the jaw, often fatal</td>
<td>Bacterium introduced in puncture wound</td>
<td>Penicillin, antitoxin</td>
<td>DTap, Tdap</td>
</tr>
</tbody>
</table>

**Figure 26.12**
26.3 Acellular Diseases of the Nervous System

Learning Objectives

• Identify the most common acellular pathogens that can cause infections of the nervous system

• Compare the major characteristics of specific viral diseases affecting the nervous system

A number of different viruses and subviral particles can cause diseases that affect the nervous system. Viral diseases tend to be more common than bacterial infections of the nervous system today. Fortunately, viral infections are generally milder than their bacterial counterparts and often spontaneously resolve. Some of the more important acellular pathogens of the nervous system are described in this section.

Viral Meningitis

Although it is much more common than bacterial meningitis, viral meningitis is typically less severe. Many different viruses can lead to meningitis as a sequela of the primary infection, including those that cause herpes, influenza, measles, and mumps. Most cases of viral meningitis spontaneously resolve, but severe cases do occur.

Arboviral Encephalitis

Several types of insect-borne viruses can cause encephalitis. Collectively, these viruses are referred to as arboviruses (because they are arthropod-borne), and the diseases they cause are described as arboviral encephalitis. Most arboviruses are endemic to specific geographical regions. Arboviral encephalitis diseases found in the United States include eastern equine encephalitis (EEE), western equine encephalitis (WEE), St. Louis encephalitis, and West Nile encephalitis (WNE). Expansion of arboviruses beyond their endemic regions sometimes occurs, generally as a result of environmental changes that are favorable to the virus or its vector. Increased travel of infected humans, animals, or vectors has also allowed arboviruses to spread into new regions.

In most cases, arboviral infections are asymptomatic or lead to a mild disease. However, when symptoms do occur, they include high fever, chills, headaches, vomiting, diarrhea, and restlessness. In elderly patients, severe arboviral encephalitis can rapidly lead to convulsions, coma, and death.

Mosquitoes are the most common biological vectors for arboviruses, which tend to be enveloped ssRNA viruses. Thus, prevention of arboviral infections is best achieved by avoiding mosquitoes—using insect repellent, wearing long pants and sleeves, sleeping in well-screened rooms, using bed nets, etc.

Diagnosis of arboviral encephalitis is based on clinical symptoms and serologic testing of serum or CSF. There are no antiviral drugs to treat any of these arboviral diseases, so treatment consists of supportive care and management of symptoms.

Eastern equine encephalitis (EEE) is caused by eastern equine encephalitis virus (EEEV), which can cause severe disease in horses and humans. Birds are reservoirs for EEEV with accidental transmission to horses and humans by Aedes, Coquillettidia, and Culex species of mosquitoes. Neither horses nor humans serve as reservoirs. EEE is most common in US Gulf Coast and Atlantic states. EEE is one of the more severe mosquito-transmitted diseases in the United States, but fortunately, it is a very rare disease in the United States (Figure 26.13).[19][20]

Western equine encephalitis (WEE) is caused by western equine encephalitis virus (WEEV). WEEV is usually transmitted to horses and humans by the Culex tarsalis mosquitoes and, in the past decade, has caused very few cases of encephalitis in humans in the United States. In humans, WEE symptoms are less severe than EEE and include

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fever, chills, and vomiting, with a mortality rate of 3–4%. Like EEEV, birds are the natural reservoir for WEEV. Periodically, for indeterminate reasons, epidemics in human cases have occurred in North America in the past. The largest on record was in 1941, with more than 3400 cases.\[^{21}\]

![Figure 26.13](image)

**Figure 26.13** (a) A false color TEM of a mosquito salivary gland cell shows an infection of the eastern equine encephalitis virus (red). (b) CT (left) and MRI (right) scans of the brains of children with eastern equine encephalitis infections, showing abnormalities (arrows) resulting from the infection. (credit a, b: modifications of work by the Centers for Disease Control and Prevention)

**St. Louis encephalitis (SLE)**, caused by St. Louis encephalitis virus (SLEV), is a rare form of encephalitis with symptoms occurring in fewer than 1% of infected patients. The natural reservoirs for SLEV are birds. SLEV is most often found in the Ohio-Mississippi River basin of the central United States and was named after a severe outbreak in Missouri in 1934. The worst outbreak of St. Louis encephalitis occurred in 1975, with over 2000 cases reported.\[^{22}\] Humans become infected when bitten by *C. tarsalis*, *C. quinquefasciatus*, or *C. pipiens* mosquitoes carrying SLEV. Most patients are asymptomatic, but in a small number of individuals, symptoms range from mild flu-like syndromes to fatal encephalitis. The overall mortality rate for symptomatic patients is 5–15%.\[^{23}\]

**Japanese encephalitis**, caused by Japanese encephalitis virus (JEV), is the leading cause of vaccine-preventable encephalitis in humans and is endemic to some of the most populous countries in the world, including China, India, Japan, and all of Southeast Asia. JEV is transmitted to humans by *Culex* mosquitoes, usually the species *C. tritaeniorhynchus*. The biological reservoirs for JEV include pigs and wading birds. Most patients with JEV infections are asymptomatic, with symptoms occurring in fewer than 1% of infected individuals. However, about 25% of those who develop encephalitis die, and among those who recover, 30–50% have psychiatric, neurologic, or cognitive impairment.\[^{24}\] Fortunately, there is an effective vaccine that can prevent infection with JEV. The CDC recommends this vaccine for travelers who expect to spend more than one month in endemic areas.

As the name suggests, West Nile virus (WNV) and its associated disease, **West Nile encephalitis (WNE)**, did not originate in North America. Until 1999, it was endemic in the Middle East, Africa, and Asia; however, the first US


cases were identified in New York in 1999, and by 2004, the virus had spread across the entire continental United States. Over 35,000 cases, including 1400 deaths, were confirmed in the five-year period between 1999 and 2004. WNV infection remains reportable to the CDC.

WNV is transmitted to humans by Culex mosquitoes from its natural reservoir, infected birds, with 70–80% of infected patients experiencing no symptoms. Most symptomatic cases involve only mild, flu-like symptoms, but fewer than 1% of infected people develop severe and sometimes fatal encephalitis or meningitis. The mortality rate in WNV patients who develop neurological disease is about 10%. More information about West Nile virus can be found in Modes of Disease Transmission.

This interactive map (https://www.openstax.org/l/22arboviralUS) identifies cases of several arboviral diseases in humans and reservoir species by state and year for the United States.

Check Your Understanding

- Why is it unlikely that arboviral encephalitis viruses will be eradicated in the future?
- Which is the most common form of viral encephalitis in the United States?

Clinical Focus

Part 2

Levofloxacin is a quinolone antibiotic that is often prescribed to treat bacterial infections of the respiratory tract, including pneumonia and bronchitis. But after taking the medication for a week, David returned to his physician sicker than before. He claimed that the antibiotic had no effect on his earlier symptoms. In addition, he now was experiencing headaches, a stiff neck, and difficulty focusing at work. He also showed the doctor a rash that had developed on his arms over the past week. His doctor, more concerned now, began to ask about David's activities over the past two weeks.

David explained that he had been recently working on a project to disassemble an old barn. His doctor collected sputum samples and scrapings from David's rash for cultures. A spinal tap was also performed to examine David's CSF. Microscopic examination of his CSF revealed encapsulated yeast cells. Based on this result, the doctor prescribed a new antimicrobial therapy using amphotericin B and flucytosine.

- Why was the original treatment ineffective?
- Why is the presence of a capsule clinically important?

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

Zika Virus Infection

Zika virus infection is an emerging arboviral disease associated with human illness in Africa, Southeast Asia, and South and Central America; however, its range is expanding as a result of the widespread range of its mosquito vector. The first cases originating in the United States were reported in 2016. The Zika virus was initially described
in 1947 from monkeys in the Zika Forest of Uganda through a network that monitored yellow fever. It was not considered a serious human pathogen until the first large-scale outbreaks occurred in Micronesia in 2007; however, the virus has gained notoriety over the past decade, as it has emerged as a cause of symptoms similar to other arboviral infections that include fever, skin rashes, conjunctivitis, muscle and joint pain, malaise, and headache. Mosquitoes of the Aedes genus are the primary vectors, although the virus can also be transmitted sexually, from mother to baby during pregnancy, or through a blood transfusion.

Most Zika virus infections result in mild symptoms such as fever, a slight rash, or conjunctivitis. However, infections in pregnant women can adversely affect the developing fetus. Reports in 2015 indicate fetal infections can result in brain damage, including a serious birth defect called microcephaly, in which the infant is born with an abnormally small head (Figure 26.14).

Diagnosis of Zika is primarily based on clinical symptoms. However, the FDA recently authorized the use of a Zika virus RNA assay, Trioplex RT-PCR, and Zika MAC-ELISA to test patient blood and urine to confirm Zika virus disease. There are currently no antiviral treatments or vaccines for Zika virus, and treatment is limited to supportive care.

Figure 26.14  (a) This colorized electron micrograph shows Zika virus particles (red). (b) Women infected by the Zika virus during pregnancy may give birth to children with microcephaly, a deformity characterized by an abnormally small head and brain. (credit a, b: modifications of work by the Centers for Disease Control and Prevention)

Check Your Understanding

- What are the signs and symptoms of Zika virus infection in adults?
- Why is Zika virus infection considered a serious public health threat?

Rabies

Rabies is a deadly zoonotic disease that has been known since antiquity. The disease is caused by rabies virus (RV), a member of the family Rhabdoviridae, and is primarily transmitted through the bite of an infected mammal. Rhabdoviridae are enveloped RNA viruses that have a distinctive bullet shape (Figure 26.15); they were first studied


by Louis Pasteur, who obtained rabies virus from rabid dogs and cultivated the virus in rabbits. He successfully prepared a rabies vaccine using dried nerve tissues from infected animals. This vaccine was used to first treat an infected human in 1885.

The most common reservoirs in the United States are wild animals such as raccoons (30.2% of all animal cases during 2014), bats (29.1%), skunks (26.3%), and foxes (4.1%); collectively, these animals were responsible for a total of 92.6% of animal rabies cases in the United States in 2014. The remaining 7.4% of cases that year were in domesticated animals such as dogs, cats, horses, mules, sheep, goats, and llamas. While there are typically only one or two human cases per year in the United States, rabies still causes tens of thousands of human deaths per year worldwide, primarily in Asia and Africa.

The low incidence of rabies in the United States is primarily a result of the widespread vaccination of dogs and cats. An oral vaccine is also used to protect wild animals, such as raccoons and foxes, from infection. Oral vaccine programs tend to focus on geographic areas where rabies is endemic. The oral vaccine is usually delivered in a package of bait that is dropped by airplane, although baiting in urban areas is done by hand to maximize safety. Many countries require a quarantine or proof of rabies vaccination for domestic pets being brought into the country. These procedures are especially strict in island nations where rabies is not yet present, such as Australia.

The incubation period for rabies can be lengthy, ranging from several weeks or months to over a year. As the virus replicates, it moves from the site of the bite into motor and sensory axons of peripheral nerves and spreads from nerve to nerve using a process called retrograde transport, eventually making its way to the CNS through the spinal ganglia. Once rabies virus reaches the brain, the infection leads to encephalitis caused by the disruption of normal neurotransmitter function, resulting in the symptoms associated with rabies. The virions act in the synaptic spaces as competitors with a variety of neurotransmitters for acetylcholine, GABA, and glycine receptors. Thus, the action of rabies virus is neurotoxic rather than cytotoxic. After the rabies virus infects the brain, it can continue to spread through other neuronal pathways, traveling out of the CNS to tissues such as the salivary glands, where the virus can be released. As a result, as the disease progresses the virus can be found in many other tissues, including the salivary glands, taste buds, nasal cavity, and tears.

The early symptoms of rabies include discomfort at the site of the bite, fever, and headache. Once the virus reaches the brain and later symptoms appear, the disease is always fatal. Terminal rabies cases can end in one of two ways: either furious or paralytic rabies. Individuals with furious rabies become very agitated and hyperactive. Hydrophobia (a fear of water) is common in patients with furious rabies, which is caused by muscular spasms in the throat when swallowing or thinking about water. Excess salivation and a desire to bite can lead to foaming of the mouth. These behaviors serve to enhance the likelihood of viral transmission, although contact with infected secretions like saliva or tears alone is sufficient for infection. The disease culminates after just a few days with terror and confusion, followed by cardiovascular and respiratory arrest. In contrast, individuals with paralytic rabies generally follow a longer course of disease. The muscles at the site of infection become paralyzed. Over a period of time, the paralysis slowly spreads throughout the body. This paralytic form of disease culminates in coma and death.

Before present-day diagnostic methods were available, rabies diagnosis was made using a clinical case history and histopathological examination of biopsy or autopsy tissues, looking for the presence of Negri bodies. We now know these histologic changes cannot be used to confirm a rabies diagnosis. There are no tests that can detect rabies virus in humans at the time of the bite or shortly thereafter. Once the virus has begun to replicate (but before clinical symptoms occur), the virus can be detected using an immunofluorescence test on cutaneous nerves found at the base of hair follicles. Saliva can also be tested for viral genetic material by reverse transcription followed by polymerase chain reaction (RT-PCR). Even when these tests are performed, most suspected infections are treated as positive in the

absence of contravening evidence. It is better that patients undergo unnecessary therapy because of a false-positive result, rather than die as the result of a false-negative result.

Human rabies infections are treated by immunization with multiple doses of an attenuated vaccine to develop active immunity in the patient (see the Clinical Focus feature in the chapter on Acellular Pathogens). Vaccination of an already-infected individual has the potential to work because of the slow progress of the disease, which allows time for the patient’s immune system to develop antibodies against the virus. Patients may also be treated with human rabies immune globulin (antibodies to the rabies virus) to encourage passive immunity. These antibodies will neutralize any free viral particles. Although the rabies infection progresses slowly in peripheral tissues, patients are not normally able to mount a protective immune response on their own.

Figure 26.15  Virions of the rabies virus have a characteristic bullet-like shape. (credit: modification of work by the Centers for Disease Control and Prevention)

Check Your Understanding

- How does the bite from an infected animal transmit rabies?
- What is the goal of wildlife vaccination programs for rabies?
- How is rabies treated in a human?

Poliomyelitis

Poliomyelitis (polio), caused by poliovirus, is a primarily intestinal disease that, in a small percentage of cases, proceeds to the nervous system, causing paralysis and, potentially, death. Poliovirus is highly contagious, with transmission occurring by the fecal-oral route or by aerosol or droplet transmission. Approximately 72% of all poliovirus infections are asymptomatic; another 25% result only in mild intestinal disease, producing nausea, fever, and headache. However, even in the absence of symptoms, patients infected with the virus can shed it in feces and oral secretions, potentially transmitting the virus to others. In about one case in every 200, the poliovirus affects cells in the CNS.

After it enters through the mouth, initial replication of poliovirus occurs at the site of implantation in the pharynx and gastrointestinal tract. As the infection progresses, poliovirus is usually present in the throat and in the stool before the onset of symptoms. One week after the onset of symptoms, there is less poliovirus in the throat, but for several weeks, poliovirus continues to be excreted in the stool. Poliovirus invades local lymphoid tissue, enters the bloodstream, and then may infect cells of the CNS. Replication of poliovirus in motor neurons of the anterior horn cells in the spinal cord, brain stem, or motor cortex results in cell destruction and leads to flaccid paralysis. In severe cases, this can involve the respiratory system, leading to death. Patients with impaired respiratory function are treated using positive-pressure ventilation systems. In the past, patients were sometimes confined to Emerson respirators, also known as iron lungs (Figure 26.16).

Direct detection of the poliovirus from the throat or feces can be achieved using reverse transcriptase PCR (RT-PCR) or genomic sequencing to identify the genotype of the poliovirus infecting the patient. Serological tests can be used to determine whether the patient has been previously vaccinated. There are no therapeutic measures for polio; treatment is limited to various supportive measures. These include pain relievers, rest, heat therapy to ease muscle spasms, physical therapy and corrective braces if necessary to help with walking, and mechanical ventilation to assist with breathing if necessary.

Figure 26.16  (a) An Emerson respiratory (or iron lung) that was used to help some polio victims to breathe. (b) Polio can also result in impaired motor function. (credit b: modification of work by the Centers for Disease Control and Prevention)

Two different vaccines were introduced in the 1950s that have led to the dramatic decrease in polio worldwide (Figure 26.17). The Salk vaccine is an inactivated polio virus that was first introduced in 1955. This vaccine is delivered by intramuscular injection. The Sabin vaccine is an oral polio vaccine that contains an attenuated virus; it was licensed for use in 1962. There are three serotypes of poliovirus that cause disease in humans; both the Salk and the Sabin vaccines are effective against all three.

Attenuated viruses from the Sabin vaccine are shed in the feces of immunized individuals and thus have the potential to infect nonimmunized individuals. By the late 1990s, the few polio cases originating in the United States could be traced back to the Sabin vaccine. In these cases, mutations of the attenuated virus following vaccination likely allowed the microbe to revert to a virulent form. For this reason, the United States switched exclusively to the Salk vaccine in 2000. Because the Salk vaccine contains an inactivated virus, there is no risk of transmission to others (see Vaccines). Currently four doses of the vaccine are recommended for children: at 2, 4, and 6–18 months of age, and at 4–6 years of age.

In 1988, WHO launched the Global Polio Eradication Initiative with the goal of eradicating polio worldwide through immunization. That goal is now close to being realized. Polio is now endemic in only a few countries, including Afghanistan, Pakistan, and Nigeria, where vaccination efforts have been disrupted by military conflict or political instability.
Figure 26.17  (a) Polio is caused by the poliovirus. (b) Two American virologists developed the first polio vaccines: Albert Sabin (left) and Jonas Salk (right). (credit a: modification of work by the Centers for Disease Control and Prevention)

The Terror of Polio

In the years after World War II, the United States and the Soviet Union entered a period known as the Cold War. Although there was no armed conflict, the two super powers were diplomatically and economically isolated from each other, as represented by the so-called Iron Curtain between the Soviet Union and the rest of the world. After 1950, migration or travel outside of the Soviet Union was exceedingly difficult, and it was equally difficult for foreigners to enter the Soviet Union. The United States also placed strict limits on Soviets entering the country. During the Eisenhower administration, only 20 graduate students from the Soviet Union were allowed to come to study in the United States per year.

Yet even the Iron Curtain was no match for polio. The Salk vaccine became widely available in the West in 1955, and by the time the Sabin vaccine was ready for clinical trials, most of the susceptible population in the United States and Canada had already been vaccinated against polio. Sabin needed to look elsewhere for study participants. At the height of the Cold War, Mikhail Chumakov was allowed to come to the United States to study Sabin’s work. Likewise, Sabin, an American microbiologist, was allowed to travel to the Soviet Union to begin clinical trials. Chumakov organized Soviet-based production and managed the experimental trials to test the new vaccine in the Soviet Union. By 1959, over ten million Soviet children had been safely treated with Sabin’s vaccine.

As a result of a global vaccination campaign with the Sabin vaccine, the overall incidence of polio has dropped dramatically. Today, polio has been nearly eliminated around the world and is only rarely seen in the United States. Perhaps one day soon, polio will become the third microbial disease to be eradicated from the general population [small pox and rinderpest (the cause of cattle plague) being the first two].

Check Your Understanding

- How is poliovirus transmitted?
Transmissible Spongiform Encephalopathies

Acellular infectious agents called prions are responsible for a group of related diseases known as transmissible spongiform encephalopathies (TSEs) that occurs in humans and other animals (see Viroids, Virusoids, and Prions). All TSEs are degenerative, fatal neurological diseases that occur when brain tissue becomes infected by prions. These diseases have a slow onset; symptoms may not become apparent until after an incubation period of years and perhaps decades, but death usually occurs within months to a few years after the first symptoms appear.

TSEs in animals include scrapie, a disease in sheep that has been known since the 1700s, and chronic wasting disease, a disease of deer and elk in the United States and Canada. Mad cow disease is seen in cattle and can be transmitted to humans through the consumption of infected nerve tissues. Human prion diseases include Creutzfeldt-Jakob disease and kuru, a rare disease endemic to Papua New Guinea.

Prions are infectious proteinaceous particles that are not viruses and do not contain nucleic acid. They are typically transmitted by exposure to and ingestion of infected nervous system tissues, tissue transplants, blood transfusions, or contaminated fomites. Prion proteins are normally found in a healthy brain tissue in a form called PrP\textsubscript{C}. However, if this protein is misfolded into a denatured form (PrP\textsubscript{Sc}), it can cause disease. Although the exact function of PrP\textsubscript{C} is not currently understood, the protein folds into mostly alpha helices and binds copper. The rogue protein, on the other hand, folds predominantly into beta-pleated sheets and is resistant to proteolysis. In addition, PrP\textsubscript{Sc} can induce PrP\textsubscript{C} to become misfolded and produce more rogue protein (Figure 26.18).

As PrP\textsubscript{Sc} accumulates, it aggregates and forms fibrils within nerve cells. These protein complexes ultimately cause the cells to die. As a consequence, brain tissues of infected individuals form masses of neurofibrillary tangles and amyloid plaques that give the brain a spongy appearance, which is why these diseases are called spongiform encephalopathy (Figure 6.26). Damage to brain tissue results in a variety of neurological symptoms. Most commonly, affected individuals suffer from memory loss, personality changes, blurred vision, uncoordinated movements, and insomnia. These symptoms gradually worsen over time and culminate in coma and death.

The gold standard for diagnosing TSE is the histological examination of brain biopsies for the presence of characteristic amyloid plaques, vacuoles, and prion proteins. Great care must be taken by clinicians when handling suspected prion-infected materials to avoid becoming infected themselves. Other tissue assays search for the presence of the 14-3-3 protein, a marker for prion diseases like Creutzfeldt-Jakob disease. New assays, like RT-QuIC (real-time quaking-induced conversion), offer new hope to effectively detect the abnormal prion proteins in tissues earlier in the course of infection. Prion diseases cannot be cured. However, some medications may help slow their progress. Medical support is focused on keeping patients as comfortable as possible despite progressive and debilitating symptoms.

**Figure 26.18** The replicative cycle of misfolded prion proteins.
Because prion-contaminated materials are potential sources of infection for clinical scientists and physicians, both the World Health Organization (https://www.openstax.org/l/22WHOprion) and CDC (https://www.openstax.org/l/22CDCprion) provide information to inform, educate and minimize the risk of infections due to prions.

Check Your Understanding

- Do prions reproduce in the conventional sense?
- What is the connection between prions and the removal of animal byproducts from the food of farm animals?

Disease Profile

Acellular Infections of the Nervous System

Serious consequences are the common thread among these neurological diseases. Several cause debilitating paralysis, and some, such as Creutzfeldt-Jakob disease and rabies, are always or nearly always fatal. Since few drugs are available to combat these infections, vector control and vaccination are critical for prevention and containment. Figure 26.19 summarizes some important viral and prion infections of the nervous system.
<table>
<thead>
<tr>
<th>Disease</th>
<th>Pathogen</th>
<th>Signs and Symptoms</th>
<th>Transmission</th>
<th>Diagnostic Tests</th>
<th>Antimicrobial Drugs</th>
<th>Vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arboviral encephalitis (eastern equine, western equine, St. Louis, West Nile, Japanese)</td>
<td>EEEV, WEEV, SLEV, WNV, JEV</td>
<td>In mild cases, fever, chills, headaches, and restlessness; in serious cases, encephalitis leading to convulsions, coma, and death</td>
<td>From bird reservoirs to humans (and horses) by mosquito vectors of various species</td>
<td>Serologic testing of serum or CSF</td>
<td>None</td>
<td>Human vaccine available for JEV only; no vaccines available for other arboviruses</td>
</tr>
<tr>
<td>Creutzfeldt-Jacob Disease and other TSEs</td>
<td>Prions</td>
<td>Memory loss, confusion, blurred vision, uncoordinated movement, insomnia, coma, death</td>
<td>Exposure to infected nerve tissue via consumption or transplant, inherited</td>
<td>Tissue biopsy</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Poliomyelitis</td>
<td>Poliovirus</td>
<td>Asymptomatic or mild nausea, fever, headache in most cases; in neurological infections, flaccid paralysis and potentially fatal respiratory paralysis</td>
<td>Fecal-oral route or contact with droplets or aerosols</td>
<td>Culture of poliovirus, PCR</td>
<td>None</td>
<td>Attenuated vaccine (Sabin), killed vaccine (Salk)</td>
</tr>
<tr>
<td>Rabies</td>
<td>Rabies virus (RV)</td>
<td>Fever, headaches, hyperactivity, hydrophobia, excessive salivation, terrors, confusion, spreading paralysis, coma, always fatal if not promptly treated</td>
<td>From bite of infected mammal</td>
<td>Viral antigen in tissue, antibodies to virus</td>
<td>Attenuated vaccine</td>
<td>Attenuated vaccine</td>
</tr>
<tr>
<td>Viral meningitis</td>
<td>HSV-1, HSV-2, varicella zoster virus, mumps virus, influenza virus, measles virus</td>
<td>Nausea, vomiting, photophobia, stiff neck, confusion, symptoms generally resolve within 7–10 days</td>
<td>Sequela of primary viral infection</td>
<td>Varies depending on cause</td>
<td>Varies depending on cause</td>
<td></td>
</tr>
<tr>
<td>Zika virus infection</td>
<td>Zika virus</td>
<td>Fever, rash, conjunctivitis; in pregnant women, can cause fetal brain damage and microcephaly</td>
<td>Between humans by Aedes spp. mosquito vectors, also may be transmitted sexually or via blood transfusion</td>
<td>Zika virus RNA assay, Trioplex RT-PCR, Zika MAC-ELISA test</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>
26.4 Fungal and Parasitic Diseases of the Nervous System

Learning Objectives
• Identify the most common fungi that can cause infections of the nervous system
• Compare the major characteristics of specific fungal diseases affecting the nervous system

Fungal infections of the nervous system, called neuromycoses, are rare in healthy individuals. However, neuromycoses can be devastating in immunocompromised or elderly patients. Several eukaryotic parasites are also capable of infecting the nervous system of human hosts. Although relatively uncommon, these infections can also be life-threatening in immunocompromised individuals. In this section, we will first discuss neuromycoses, followed by parasitic infections of the nervous system.

Cryptococcocal Meningitis

*Cryptococcus neoformans* is a fungal pathogen that can cause meningitis. This yeast is commonly found in soils and is particularly associated with pigeon droppings. It has a thick capsule that serves as an important virulence factor, inhibiting clearance by phagocytosis. Most *C. neoformans* cases result in subclinical respiratory infections that, in healthy individuals, generally resolve spontaneously with no long-term consequences (see Respiratory Mycoses). In immunocompromised patients or those with other underlying illnesses, the infection can progress to cause meningitis and granuloma formation in brain tissues. *Cryptococcus* antigens can also serve to inhibit cell-mediated immunity and delayed-type hypersensitivity.

*Cryptococcus* can be easily cultured in the laboratory and identified based on its extensive capsule (Figure 26.20). *C. neoformans* is frequently cultured from urine samples of patients with disseminated infections.

Prolonged treatment with antifungal drugs is required to treat cryptococcal infections. Combined therapy is required with amphotericin B plus flucytosine for at least 10 weeks. Many antifungal drugs have difficulty crossing the blood-brain barrier and have strong side effects that necessitate low doses; these factors contribute to the lengthy time of treatment. Patients with AIDS are particularly susceptible to *Cryptococcus* infections because of their compromised immune state. AIDS patients with cryptococcosis can also be treated with antifungal drugs, but they often have relapses; lifelong doses of fluconazole may be necessary to prevent reinfection.

![Figure 26.20](credit: modification of work by Centers for Disease Control and Prevention)
Check Your Understanding

- Why are neuromycoses infections rare in the general population?
- How is a cryptococcal infection acquired?

Disease Profile

Neuromycoses

Neuromycoses typically occur only in immunocompromised individuals and usually only invade the nervous system after first infecting a different body system. As such, many diseases that sometimes affect the nervous system have already been discussed in previous chapters. Figure 26.21 presents some of the most common fungal infections associated with neurological disease. This table includes only the neurological aspects associated with these diseases; it does not include characteristics associated with other body systems.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Pathogen</th>
<th>Signs and Symptoms</th>
<th>Transmission</th>
<th>Diagnostic Tests</th>
<th>Antimicrobial Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspergillosis</td>
<td><em>Aspergillus fumigatus</em></td>
<td>Meningitis, brain abscesses</td>
<td>Dissemination from respiratory infection</td>
<td>CSF, routine culture</td>
<td>Amphotericin B, voriconazole</td>
</tr>
<tr>
<td>Candidiasis</td>
<td><em>Candida albicans</em></td>
<td>Meningitis</td>
<td>Oropharynx or urogenital</td>
<td>CSF, routine culture</td>
<td>Amphotericin B, flucytosine</td>
</tr>
<tr>
<td>Coccidioidomycosis</td>
<td><em>Coccidioides immitis</em></td>
<td>Meningitis (in about 1% of infections)</td>
<td>Dissemination from respiratory infection</td>
<td>CSF, routine culture</td>
<td>Amphotericin B, azoles</td>
</tr>
<tr>
<td>Cryptococcosis</td>
<td><em>Cryptococcus neoformans</em></td>
<td>Meningitis, granuloma formation in brain</td>
<td>Inhalation</td>
<td>Negative stain of CSF, routine culture</td>
<td>Amphotericin B, flucytosine</td>
</tr>
<tr>
<td>Histoplasmosis</td>
<td><em>Histoplasma capsulatum</em></td>
<td>Meningitis, granulomas in the brain</td>
<td>Dissemination from respiratory infection</td>
<td>CSF, routine culture</td>
<td>Amphotericin B, itraconazole</td>
</tr>
<tr>
<td>Mucormycosis</td>
<td><em>Rhizopus arrhizus</em></td>
<td>Brain abscess</td>
<td>Nasopharynx</td>
<td>CSF, routine culture</td>
<td>Amphotericin B, azoles</td>
</tr>
</tbody>
</table>

Figure 26.21

Clinical Focus

Resolution

David’s new prescription for two antifungal drugs, amphotericin B and flucytosine, proved effective, and his condition began to improve. Culture results from David’s sputum, skin, and CSF samples confirmed a fungal infection. All were positive for *C. neoformans*. Serological tests of his tissues were also positive for the *C. neoformans* capsular polysaccharide antigen.
Since *C. neoformans* is known to occur in bird droppings, it is likely that David had been exposed to the fungus while working on the barn. Despite this exposure, David’s doctor explained to him that immunocompetent people rarely contract cryptococcal meningitis and that his immune system had likely been compromised by the anti-inflammatory medication he was taking to treat his Crohn’s disease. However, to rule out other possible causes of immunodeficiency, David’s doctor recommended that he be tested for HIV.

After David tested negative for HIV, his doctor took him off the corticosteroid he was using to manage his Crohn’s disease, replacing it with a different class of drug. After several weeks of antifungal treatments, David managed a full recovery.

Jump to the previous Clinical Focus box.

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**Amoebic Meningitis**

Primary amoebic meningoencephalitis (PAM) is caused by *Naegleria fowleri*. This amoeboflagellate is commonly found free-living in soils and water. It can exist in one of three forms—the infective amoebic trophozoite form, a motile flagellate form, and a resting cyst form. PAM is a rare disease that has been associated with young and otherwise healthy individuals. Individuals are typically infected by the amoeba while swimming in warm bodies of freshwater such as rivers, lakes, and hot springs. The pathogenic trophozoite infects the brain by initially entering through nasal passages to the sinuses; it then moves down olfactory nerve fibers to penetrate the submucosal nervous plexus, invades the cribriform plate, and reaches the subarachnoid space. The subarachnoid space is highly vascularized and is a route of dissemination of trophozoites to other areas of the CNS, including the brain ([Figure 26.22](#)). Inflammation and destruction of gray matter leads to severe headaches and fever. Within days, confusion and convulsions occur and quickly progress to seizures, coma, and death. The progression can be very rapid, and the disease is often not diagnosed until autopsy.

*N. fowleri* infections can be confirmed by direct observation of CSF; the amoebae can often be seen moving while viewing a fresh CSF wet mount through a microscope. Flagellated forms can occasionally also be found in CSF. The amoebae can be stained with several stains for identification, including Giemsa-Wright or a modified trichrome stain. Detection of antigens with indirect immunofluorescence, or genetic analysis with PCR, can be used to confirm an initial diagnosis. *N. fowleri* infections are nearly always fatal; only 3 of 138 patients with PAM in the United States have survived.\(^{32}\)

A new experimental drug called miltefosine shows some promise for treating these infections. This drug is a phosphotidylcholine derivative that is thought to inhibit membrane function in *N. fowleri*, triggering apoptosis and disturbance of lipid-dependent cell signaling pathways.\(^{33}\) When administered early in infection and coupled with therapeutic hypothermia (lowering the body’s core temperature to reduce the cerebral edema associated with infection), this drug has been successfully used to treat primary amoebic encephalitis.


Granulomatous Amoebic Encephalitis

*Acanthamoeba* and *Balamuthia* species are free-living amoebae found in many bodies of fresh water. Human infections by these amoebae are rare. However, they can cause amoebic keratitis in contact lens wearers (see *Protozoan and Helminthic Infections of the Eyes*), disseminated infections in immunocompromised patients, and **granulomatous amoebic encephalitis (GAE)** in severe cases. Compared to PAM, GAE tend to be subacute infections. The microbe is thought to enter through either the nasal sinuses or breaks in the skin. It is disseminated hematogenously and can invade the CNS. There, the infections lead to inflammation, formation of lesions, and development of typical neurological symptoms of encephalitis (Figure 26.23). GAE is nearly always fatal.

GAE is often not diagnosed until late in the infection. Lesions caused by the infection can be detected using CT or MRI. The live amoebae can be directly detected in CSF or tissue biopsies. Serological tests are available but generally are not necessary to make a correct diagnosis, since the presence of the organism in CSF is definitive. Some antifungal drugs, like fluconazole, have been used to treat acanthamoebal infections. In addition, a combination of miltefosine and voriconazole (an inhibitor of ergosterol biosynthesis) has recently been used to successfully treat GAE. Even with treatment, however, the mortality rate for patients with these infections is high.
How is granulomatous amoebic encephalitis diagnosed?

Human African Trypanosomiasis

Human African trypanosomiasis (also known as African sleeping sickness) is a serious disease endemic to two distinct regions in sub-Saharan Africa. It is caused by the insect-borne hemoflagellate Trypanosoma brucei. The subspecies Trypanosoma brucei rhodesiense causes East African trypanosomiasis (EAT), and another subspecies, Trypanosoma brucei gambiense causes West African trypanosomiasis (WAT). A few hundred cases of EAT are currently reported each year. WAT is more commonly reported and tends to be a more chronic disease. Around 7000 to 10,000 new cases of WAT are identified each year.

T. brucei is primarily transmitted to humans by the bite of the tsetse fly (Glossina spp.). Soon after the bite of a tsetse fly, a chancre forms at the site of infection. The flagellates then spread, moving into the circulatory system (Figure 26.24). These systemic infections result in an undulating fever, during which symptoms persist for two or three days with remissions of about a week between bouts. As the disease enters its final phase, the pathogens move from the lymphatics into the CNS. Neurological symptoms include daytime sleepiness, insomnia, and mental deterioration. In EAT, the disease runs its course over a span of weeks to months. In contrast, WAT often occurs over a span of months to years.

Although a strong immune response is mounted against the trypanosome, it is not sufficient to eliminate the pathogen. Through antigenic variation, Trypanosoma can change their surface proteins into over 100 serological types. This variation leads to the undulating form of the initial disease. The initial septicemia caused by the infection leads to high fevers. As the immune system responds to the infection, the number of organisms decrease, and the clinical symptoms abate. However, a subpopulation of the pathogen then alters its surface coat antigens by antigenic variation and evades the immune response. These flagellates rapidly proliferate and cause another bout of disease. If untreated, these infections are usually fatal.

Clinical symptoms can be used to recognize the early signs of African trypanosomiasis. These include the formation of a chancre at the site of infection and Winterbottom’s sign. Winterbottom’s sign refers to the enlargement of lymph nodes on the back of the neck—often indicative of cerebral infections. Trypanosoma can be directly observed in stained samples including blood, lymph, CSF, and skin biopsies of chancres from patients. Antibodies against the parasite are found in most patients with acute or chronic disease. Serologic testing is generally not used for diagnosis, however, since the microscopic detection of the parasite is sufficient. Early diagnosis is important for treatment. Before the nervous system is involved, drugs like pentamidine (an inhibitor of nuclear metabolism) and suramin (mechanism unclear) can be used. These drugs have fewer side effects than the drugs needed to treat the second stage of the disease. Once the sleeping sickness phase has begun, harsher drugs including melarsoprol (an arsenic derivative) and efornithine can be effective. Following successful treatment, patients still need to have follow-up examinations of their CSF for two years to detect possible relapses of the disease. The most effective means of preventing these diseases is to control the insect vector populations.

Trypanosoma brucei, the causative agent of African sleeping sickness, in a human blood smear. (credit: modification of work by the Centers for Disease Control and Prevention)

Check Your Understanding

• What is the symptom of a systemic Trypanosoma infection?
• What are the symptoms of a neurological Trypanosoma infection?
• Why are trypanosome infections so difficult to eradicate?

Neurotoxoplasmosis

Toxoplasma gondii is an ubiquitous intracellular parasite that can cause neonatal infections. Cats are the definitive host, and humans can become infected after eating infected meat or, more commonly, by ingesting oocysts shed in the feces of cats (see Parasitic Infections of the Circulatory and Lymphatic Systems). T. gondii enters the circulatory system by passing between the endothelial cells of blood vessels. Most cases of toxoplasmosis are asymptomatic. However, in immunocompromised patients, neurotoxoplasmosis caused by T. gondii infections are one of the most common causes of brain abscesses. The organism is able to cross the blood-brain barrier by infecting the endothelial cells of capillaries in the brain. The parasite reproduces within these cells, a step that appears to be necessary for entry to the brain, and then causes the endothelial cell to lyse, releasing the progeny into brain tissues. This mechanism is quite different than the method it uses to enter the bloodstream in the first place.

The brain lesions associated with neurotoxoplasmosis can be detected radiographically using MRI or CAT scans (Figure 26.25). Diagnosis can be confirmed by direct observation of the organism in CSF. RT-PCR assays can also be used to detect T. gondii through genetic markers.

Treatment of neurotoxoplasmosis caused by T. gondii infections requires six weeks of multi-drug therapy with pyrimethamine, sulfadiazine, and folinic acid. Long-term maintenance doses are often required to prevent recurrence.

Figure 26.25  This *Toxoplasma gondii* cyst, observed in mouse brain tissue, contains thousands of inactive parasites. (credit: modification of work by USDA)

Check Your Understanding

- Under what conditions is *Toxoplasma* infection serious?
- How does *Toxoplasma* circumvent the blood-brain barrier?

Neurocysticercosis

Cysticercosis is a parasitic infection caused by the larval form of the pork tapeworm, *Taenia solium*. When the larvae invade the brain and spinal cord, the condition is referred to as **neurocysticercosis**. This condition affects millions of people worldwide and is the leading cause of adult onset epilepsy in the developing world.\(^{[39]}\)

The life cycle of *T. solium* is discussed in *Helminthic Infections of the Gastrointestinal Tract*. Following ingestion, the eggs hatch in the intestine to form larvae called **cysticerci**. Adult tapeworms form in the small intestine and produce eggs that are shed in the feces. These eggs can infect other individuals through fecal contamination of food or other surfaces. Eggs can also hatch within the intestine of the original patient and lead to an ongoing autoinfection. The cystercerci, can migrate to the blood and invade many tissues in the body, including the CNS.

Neurocysticercosis is usually diagnosed through noninvasive techniques. Epidemiological information can be used as an initial screen; cysticercosis is endemic in Central and South America, Africa, and Asia. Radiological imaging (MRI and CT scans) is the primary method used to diagnose neurocysticercosis; imaging can be used to detect the one- to two-centimeter cysts that form around the parasites (**Figure 26.26**). Elevated levels of eosinophils in the blood can also indicate a parasitic infection. EIA and ELISA are also used to detect antigens associated with the pathogen.

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The treatment for neurocysticercosis depends on the location, number, size, and stage of cysticerci present. Antihelminthic chemotherapy includes albendazole and praziquantel. Because these drugs kill viable cysts, they may acutely increase symptoms by provoking an inflammatory response caused by the release of *Taenia* cysticerci antigens, as the cysts are destroyed by the drugs. To alleviate this response, corticosteroids that cross the blood-brain barrier (e.g., dexamethasone) can be used to mitigate these effects. Surgical intervention may be required to remove intraventricular cysts.

**Parasitic Diseases of the Nervous System**

Parasites that successfully invade the nervous system can cause a wide range of neurological signs and symptoms. Often, they inflict lesions that can be visualized through radiologic imaging. A number of these infections are fatal, but some can be treated (with varying levels of success) by antimicrobial drugs (Figure 26.27).
Summary

26.1 Anatomy of the Nervous System

- The nervous system consists of two subsystems: the central nervous system and peripheral nervous system.
- The skull and three meninges (the dura mater, arachnoid mater, and pia mater) protect the brain.
- Tissues of the PNS and CNS are formed of cells called glial cells and neurons.
- Since the blood-brain barrier excludes most microbes, there is no normal microbiota in the CNS.
• Some pathogens have specific virulence factors that allow them to breach the blood-brain barrier. Inflammation of the brain or meninges caused by infection is called encephalitis or meningitis, respectively. These conditions can lead to blindness, deafness, coma, and death.

26.2 Bacterial Diseases of the Nervous System

• Bacterial meningitis can be caused by several species of encapsulated bacteria, including *Haemophilus influenzae*, *Neisseria meningitidis*, *Streptococcus pneumoniae*, and *Streptococcus agalactiae* (group B streptococci). *H. influenzae* affects primarily young children and neonates, *N. meningitidis* is the only communicable pathogen and mostly affects children and young adults, *S. pneumoniae* affects mostly young children, and *S. agalactiae* affects newborns during or shortly after birth.

• Symptoms of bacterial meningitis include fever, neck stiffness, headache, confusion, convulsions, coma, and death.

• Diagnosis of bacterial meningitis is made through observations and culture of organisms in CSF. Bacterial meningitis is treated with antibiotics. *H. influenzae* and *N. meningitidis* have vaccines available.

• *Clostridium* species cause neurological diseases, including botulism and tetanus, by producing potent neurotoxins that interfere with neurotransmitter release. The PNS is typically affected. Treatment of *Clostridium* infection is effective only through early diagnosis with administration of antibiotics to control the infection and antitoxins to neutralize the endotoxin before they enter cells.

• *Listeria monocytogenes* is a foodborne pathogen that can infect the CNS, causing meningitis. The infection can be spread through the placenta to a fetus. Diagnosis is through culture of blood or CSF. Treatment is with antibiotics and there is no vaccine.

• Hansen’s disease (leprosy) is caused by the intracellular parasite *Mycobacterium leprae*. Infections cause demyelination of neurons, resulting in decreased sensation in peripheral appendages and body sites. Treatment is with multi-drug antibiotic therapy, and there is no universally recognized vaccine.

26.3 Acellular Diseases of the Nervous System

• Viral meningitis is more common and generally less severe than bacterial meningitis. It can result from secondary sequelae of many viruses or be caused by infections of arboviruses.

• Various types of arboviral encephalitis are concentrated in particular geographic locations throughout the world. These mosquito-borne viral infections of the nervous system are typically mild, but they can be life-threatening in some cases.

• Zika virus is an emerging arboviral infection with generally mild symptoms in most individuals, but infections of pregnant women can cause the birth defect microcephaly.

• Polio is typically a mild intestinal infection but can be damaging or fatal if it progresses to a neurological disease.

• Rabies is nearly always fatal when untreated and remains a significant problem worldwide.

• Transmissible spongiform encephalopathies such as Creutzfeldt-Jakob disease and kuru are caused by prions. These diseases are untreatable and ultimately fatal. Similar prion diseases are found in animals.

26.4 Fungal and Parasitic Diseases of the Nervous System

• Neuromycoses are uncommon in immunocompetent people, but immunocompromised individuals with fungal infections have high mortality rates. Treatment of neuromycoses require prolonged therapy with antifungal drugs at low doses to avoid side effects and overcome the effect of the blood-brain barrier.

• Some protist infections of the nervous systems are fatal if not treated, including primary amoebic meningitis, granulomatous amoebic encephalitis, human African trypanosomiasis, and neurotoxoplasmosis.

• The various forms of amoebic encephalitis caused by the different amoebic infections are typically fatal even with treatment, but they are rare.

• African trypanosomiasis is a serious but treatable disease endemic to two distinct regions in sub-Saharan Africa caused by the insect-borne hemoflagellate *Trypanosoma brucei*.

• Neurocysticercosis is treated using antihelminthic drugs or surgery to remove the large cysts from the CNS.
Review Questions

Multiple Choice

1. What is the outermost membrane surrounding the brain called?
   a. pia mater
   b. arachnoid mater
   c. dura mater
   d. alma mater

2. What term refers to an inflammation of brain tissues?
   a. encephalitis
   b. meningitis
   c. sinusitis
   d. meningoencephalitis

3. Nerve cells form long projections called ________.
   a. soma
   b. axons
   c. dendrites
   d. synapses

4. Chemicals called ________ are stored in neurons and released when the cell is stimulated by a signal.
   a. toxins
   b. cytokines
   c. chemokines
   d. neurotransmitters

5. The central nervous system is made up of
   a. sensory organs and muscles.
   b. the brain and muscles.
   c. the sensory organs and spinal cord.
   d. the brain and spinal column.

6. Which of the following organisms causes epidemic meningitis cases at college campuses?
   a. *Haemophilus influenzae* type b
   b. *Neisseria meningitidis*
   c. *Streptococcus pneumoniae*
   d. *Listeria monocytogenes*

7. Which of the following is the most common cause of neonatal meningitis?
   a. *Haemophilus influenzae* b
   b. *Streptococcus agalactiae*
   c. *Neisseria meningitidis*
   d. *Streptococcus pneumoniae*

8. What sign/symptom would NOT be associated with infant botulism?
   a. difficulty suckling
   b. limp body
   c. stiff neck
   d. weak cry

9. Which of the following can NOT be prevented with a vaccine?
   a. tetanus
   b. pneumococcal meningitis
   c. meningococcal meningitis
   d. listeriosis

10. How is leprosy primarily transmitted from person to person?
    a. contaminated toilet seats
    b. shaking hands
    c. blowing nose
    d. sexual intercourse

11. Which of these diseases can be prevented with a vaccine for humans?
    a. eastern equine encephalitis
    b. western equine encephalitis
    c. West Nile encephalitis
    d. Japanese encephalitis

12. Which of these diseases does NOT require the introduction of foreign nucleic acid?
    a. kuru
    b. polio
    c. rabies
    d. St. Louis encephalitis

13. Which of these is true of the Sabin but NOT the Salk polio vaccine?
    a. requires four injections
    b. currently administered in the United States
    c. mimics the normal route of infection
    d. is an inactivated vaccine

14. Which of the following animals is NOT a typical reservoir for the spread of rabies?
    a. dog
    b. bat
    c. skunk
    d. chicken
15. Which of these diseases results in meningitis caused by an encapsulated yeast?
   a. cryptococcosis
   b. histoplasmosis
   c. candidiasis
   d. coccidiomycosis

16. What kind of stain is most commonly used to visualize the capsule of cryptococcus?
   a. Gram stain
   b. simple stain
   c. negative stain
   d. fluorescent stain

17. Which of the following is the causative agent of East African trypanosomiasis?
   a. Trypanosoma cruzi
   b. Trypanosoma vivax
   c. Trypanosoma brucei rhodanese
   d. Trypanosoma brucei gambiense

18. Which of the following is the causative agent of primary amoebic meningoencephalitis?
   a. Naegleria fowleri
   b. Entameba histolyticum
   c. Amoeba proteus
   d. Acanthamoeba polyphaga

19. What is the biological vector for African sleeping sickness?
   a. mosquito
   b. tsetse fly
   c. deer tick
   d. sand fly

20. How do humans usually contract neurocysticercosis?
   a. the bite of an infected arthropod
   b. exposure to contaminated cat feces
   c. swimming in contaminated water
   d. ingestion of undercooked pork

21. Which of these is the most important cause of adult onset epilepsy?
   a. neurocysticercosis
   b. neurotoxoplasmosis
   c. primary amoebic meningoencephalitis
   d. African trypanosomiasis
Matching
22. Match each strategy for microbial invasion of the CNS with its description.

___intercellular entry A. pathogen gains entry by infecting peripheral white blood cells
___transcellular entry B. pathogen bypasses the blood-brain barrier by travel along the olfactory or trigeminal cranial nerves
___leukocyte-facilitated entry C. pathogen passes through the cells of the blood-brain barrier
___nonhematogenous entry D. pathogen passes between the cells of the blood-brain barrier

Fill in the Blank
23. The cell body of a neuron is called the ________.
24. A signal is transmitted down the ________ of a nerve cell.
25. The ________ is filled with cerebrospinal fluid.
26. The ________ ________ prevents access of microbes in the blood from gaining access to the central nervous system.
27. The ________ are a set of membranes that cover and protect the brain.
28. The form of meningitis that can cause epidemics is caused by the pathogen ________.
29. The symptoms of tetanus are caused by the neurotoxin ________.
30. ________ is another name for leprosy.
31. Botulism prevents the release of the neurotransmitter ________.
32. ________ is a neurological disease that can be prevented with the DTaP vaccine.
33. Tetanus patients exhibit ________ when muscle spasms causes them to arch their backs.
34. The rogue form of the prion protein is called ________.
35. ________ are the most common reservoir for the rabies virus worldwide.
36. ________ was the scientist who developed the inactivated polio vaccine.
37. ________ is a prion disease of deer and elk.
38. The rogue form of prion protein exists primarily in the ________ conformation.
39. The ________ is the main virulence factor of Cryptococcus neoformans.
40. The drug of choice for fungal infections of the nervous system is ________.
41. The larval forms of a tapeworm are known as ________.
42. ________ sign appears as swollen lymph nodes at the back of the neck in early African trypanosomiasis.
43. ________ African trypanosomiasis causes a chronic form of sleeping sickness.
44. The definitive host for Toxoplasma gondii is ________.
45. Trypanosomes can evade the immune response through ________ variation.
Short Answer

46. Briefly describe the defenses of the brain against trauma and infection.

47. Describe how the blood-brain barrier is formed.

48. Identify the type of cell shown, as well as the following structures: axon, dendrite, myelin sheath, soma, and synapse.

![Diagram of a neuron with labeled parts A, B, C, D, and E]

49. A physician suspects the lesion and pustule pictured here are indicative of tuberculoid leprosy. If the diagnosis is correct, what microorganism would be found in a skin biopsy?

![Image of a lesion and pustule]

Figure 26.28 (credit: Centers for Disease Control and Prevention)

50. Explain how a person could contract variant Creutzfeldt-Jakob disease by consuming products from a cow with bovine spongiform encephalopathy (mad cow disease).

51. Why do nervous system infections by fungi require such long treatment times?

52. Briefly describe how humans are infected by *Naegleria fowleri*.

53. Briefly describe how humans can develop neurocysticercosis.
Critical Thinking

54. What important function does the blood-brain barrier serve? How might this barrier be problematic at times?

55. Explain how tetanospasmin functions to cause disease.

56. The most common causes of bacterial meningitis can be the result of infection by three very different bacteria. Which bacteria are they and how are these microbes similar to each other?

57. Explain how infant botulism is different than foodborne botulism.

58. If the Sabin vaccine is being used to eliminate polio worldwide, explain why a country with a near zero infection rate would opt to use the Salk vaccine but not the Sabin vaccine?

59. The graph shown tracks the body temperature of a patient infected with *Trypanosoma brucei*. How would you describe this pattern, and why does it occur?

![Graph showing temperature changes over time](credit: modification of work by Wellcome Images)

60. Fungal meningoencephalitis is often the ultimate cause of death for AIDS patients. What factors make these infections more problematic than those of bacterial origin?

Introduction

In 1954, French scientist and future Nobel laureate Jacques Monod (1910–1976) famously said, “What is true in *E. coli* is true in the elephant,” suggesting that the biochemistry of life was maintained throughout evolution and is shared in all forms of known life. Since Monod’s famous statement, we have learned a great deal about the mechanisms of gene regulation, expression, and replication in living cells. All cells use DNA for information storage, share the same genetic code, and use similar mechanisms to replicate and express it. Although many aspects of genetics are universally shared, variations do exist among contemporary genetic systems. We now know that within the shared overall theme of the genetic mechanism, there are significant differences among the three domains of life: Eukarya, Archaea, and Bacteria. Additionally, viruses, cellular parasites but not themselves living cells, show dramatic variation in their genetic material and the replication and gene expression processes. Some of these differences have allowed us to engineer clinical tools such as antibiotics and antiviral drugs that specifically inhibit the reproduction of pathogens yet are harmless to their hosts.
11.1 The Functions of Genetic Material

Learning Objectives

- Explain the two functions of the genome
- Explain the meaning of the central dogma of molecular biology
- Differentiate between genotype and phenotype and explain how environmental factors influence phenotype

DNA serves two essential functions that deal with cellular information. First, DNA is the genetic material responsible for inheritance and is passed from parent to offspring for all life on earth. To preserve the integrity of this genetic information, DNA must be replicated with great accuracy, with minimal errors that introduce changes to the DNA sequence. A genome contains the full complement of DNA within a cell and is organized into smaller, discrete units called genes that are arranged on chromosomes and plasmids. The second function of DNA is to direct and regulate the construction of the proteins necessary to a cell for growth and reproduction in a particular cellular environment.

A gene is composed of DNA that is “read” or transcribed to produce an RNA molecule during the process of transcription. One major type of RNA molecule, called messenger RNA (mRNA), provides the information for the ribosome to catalyze protein synthesis in a process called translation. The processes of transcription and translation are collectively referred to as gene expression. Gene expression is the synthesis of a specific protein with a sequence of amino acids that is encoded in the gene. The flow of genetic information from DNA to RNA to protein is described by the central dogma (Figure 11.2). This central dogma of molecular biology further elucidates the mechanism behind Beadle and Tatum’s “one gene-one enzyme” hypothesis (see Using Microorganisms to Discover the Secrets of Life). Each of the processes of replication, transcription, and translation includes the stages of 1) initiation, 2) elongation (polymerization), and 3) termination. These stages will be described in more detail in this chapter.

**Figure 11.2** The central dogma states that DNA encodes messenger RNA, which, in turn, encodes protein.

A cell’s genotype is the full collection of genes it contains, whereas its phenotype is the set of observable characteristics that result from those genes. The phenotype is the product of the array of proteins being produced by Part 1

Mark is 60-year-old software engineer who suffers from type II diabetes, which he monitors and keeps under control largely through diet and exercise. One spring morning, while doing some gardening, he scraped his lower leg while walking through blackberry brambles. He continued working all day in the yard and did not bother to clean the wound and treat it with antibiotic ointment until later that evening. For the next 2 days, his leg became increasingly red, swollen, and warm to the touch. It was sore not only on the surface, but deep in the muscle. After 24 hours, Mark developed a fever and stiffness in the affected leg. Feeling increasingly weak, he called a neighbor, who drove him to the emergency department.

- Did Mark wait too long to seek medical attention? At what point do his signs and symptoms warrant seeking medical attention?
- What types of infections or other conditions might be responsible for Mark’s symptoms?

*Jump to the next Clinical Focus box.*
the cell at a given time, which is influenced by the cell’s genotype as well as interactions with the cell’s environment. Genes code for proteins that have functions in the cell. Production of a specific protein encoded by an individual gene often results in a distinct phenotype for the cell compared with the phenotype without that protein. For this reason, it is also common to refer to the genotype of an individual gene and its phenotype. Although a cell’s genotype remains constant, not all genes are used to direct the production of their proteins simultaneously. Cells carefully regulate expression of their genes, only using genes to make specific proteins when those proteins are needed (Figure 11.3).

**Figure 11.3** Phenotype is determined by the specific genes within a genotype that are expressed under specific conditions. Although multiple cells may have the same genotype, they may exhibit a wide range of phenotypes resulting from differences in patterns of gene expression in response to different environmental conditions.

**Check Your Understanding**

- What are the two functions of DNA?
- Distinguish between the genotype and phenotype of a cell.
- How can cells have the same genotype but differ in their phenotype?

**Eye on Ethics**

**Use and Abuse of Genome Data**

Why can some humans harbor opportunistic pathogens like *Haemophilus influenzae*, *Staphylococcus aureus*, or *Streptococcus pyogenes*, in their upper respiratory tracts but remain asymptomatic carriers, while other individuals become seriously ill when infected? There is evidence suggesting that differences in susceptibility to infection between patients may be a result, at least in part, of genetic differences between human hosts. For example, genetic differences in human leukocyte antigens (HLAs) and red blood cell antigens among hosts have been implicated in different immune responses and resulting disease progression from infection with *H. influenzae*.

Because the genetic interplay between pathogen and host may contribute to disease outcomes, understanding differences in genetic makeup between individuals may be an important clinical tool. Ecological genomics is a relatively new field that seeks to understand how the genotypes of different organisms interact with each other in nature. The field answers questions about how gene expression of one organism affects gene expression of another. Medical applications of ecological genomics will focus on how pathogens interact with specific individuals, as opposed to humans in general. Such analyses would allow medical professionals to
use knowledge of an individual’s genotype to apply more individualized plans for treatment and prevention of disease.

With the advent of next-generation sequencing, it is relatively easy to obtain the entire genomic sequences of pathogens; a bacterial genome can be sequenced in as little as a day.[1] The speed and cost of sequencing the human genome has also been greatly reduced and, already, individuals can submit samples to receive extensive reports on their personal genetic traits, including ancestry and carrier status for various genetic diseases. As sequencing technologies progress further, such services will continue to become less expensive, more extensive, and quicker.

However, as this day quickly approaches, there are many ethical concerns with which society must grapple. For example, should genome sequencing be a standard practice for everybody? Should it be required by law or by employers if it will lower health-care costs? If one refuses genome sequencing, does he or she forfeit his or her right to health insurance coverage? For what purposes should the data be used? Who should oversee proper use of these data? If genome sequencing reveals predisposition to a particular disease, do insurance companies have the right to increase rates? Will employers treat an employee differently? Knowing that environmental influences also affect disease development, how should the data on the presence of a particular disease-causing allele in an individual be used ethically? The Genetic Information Nondiscrimination Act of 2008 (GINA) currently prohibits discriminatory practices based on genetic information by both health insurance companies and employers. However, GINA does not cover life, disability, or long-term care insurance policies. Clearly, all members of society must continue to engage in conversations about these issues so that such genomic data can be used to improve health care while simultaneously protecting an individual’s rights.

11.2 DNA Replication

Learning Objectives

• Explain the meaning of semiconservative DNA replication
• Explain why DNA replication is bidirectional and includes both a leading and lagging strand
• Explain why Okazaki fragments are formed
• Describe the process of DNA replication and the functions of the enzymes involved
• Identify the differences between DNA replication in bacteria and eukaryotes
• Explain the process of rolling circle replication

The elucidation of the structure of the double helix by James Watson and Francis Crick in 1953 provided a hint as to how DNA is copied during the process of replication. Separating the strands of the double helix would provide two templates for the synthesis of new complementary strands, but exactly how new DNA molecules were constructed was still unclear. In one model, semiconservative replication, the two strands of the double helix separate during DNA replication, and each strand serves as a template from which the new complementary strand is copied; after replication, each double-stranded DNA includes one parental or “old” strand and one “new” strand. There were two competing models also suggested: conservative and dispersive, which are shown in Figure 11.4.

There were three models suggested for DNA replication. In the conservative model, parental DNA strands (blue) remained associated in one DNA molecule while new daughter strands (red) remained associated in newly formed DNA molecules. In the semiconservative model, parental strands separated and directed the synthesis of a daughter strand, with each resulting DNA molecule being a hybrid of a parental strand and a daughter strand. In the dispersive model, all resulting DNA strands have regions of double-stranded parental DNA and regions of double-stranded daughter DNA.

Matthew Meselson (1930–) and Franklin Stahl (1929–) devised an experiment in 1958 to test which of these models correctly represents DNA replication (Figure 11.5). They grew *E. coli* for several generations in a medium containing a “heavy” isotope of nitrogen \(^{15}\text{N}\) that was incorporated into nitrogenous bases and, eventually, into the DNA. This labeled the parental DNA. The *E. coli* culture was then shifted into a medium containing \(^{14}\text{N}\) and allowed to grow for one generation. The cells were harvested and the DNA was isolated. The DNA was separated by ultracentrifugation, during which the DNA formed bands according to its density. DNA grown in \(^{15}\text{N}\) would be expected to form a band at a higher density position than that grown in \(^{14}\text{N}\). Meselson and Stahl noted that after one generation of growth in \(^{14}\text{N}\), the single band observed was intermediate in position in between DNA of cells grown exclusively in \(^{15}\text{N}\) or \(^{14}\text{N}\). This suggested either a semiconservative or dispersive mode of replication. Some cells were allowed to grow for one more generation in \(^{14}\text{N}\) and spun again. The DNA harvested from cells grown for two generations in \(^{14}\text{N}\) formed two bands: one DNA band was at the intermediate position between \(^{15}\text{N}\) and \(^{14}\text{N}\), and the other corresponded to the band of \(^{14}\text{N}\) DNA. These results could only be explained if DNA replicates in a semiconservative manner. Therefore, the other two models were ruled out. As a result of this experiment, we now know that during DNA replication, each of the two strands that make up the double helix serves as a template from which new strands are copied. The new strand will be complementary to the parental or “old” strand. The resulting DNA molecules have the same sequence and are divided equally into the two daughter cells.
Meselson and Stahl experimented with *E. coli* grown first in heavy nitrogen (\(^{15}\text{N}\)) then in \(^{14}\text{N}\). DNA grown in \(^{15}\text{N}\) (blue band) was heavier than DNA grown in \(^{14}\text{N}\) (red band), and sedimented to a lower level on ultracentrifugation. After one round of replication, the DNA sedimented halfway between the \(^{15}\text{N}\) and \(^{14}\text{N}\) levels (purple band), ruling out the conservative model of replication. After a second round of replication, the dispersive model of replication was ruled out. These data supported the semiconservative replication model.

**Check Your Understanding**

- What would have been the conclusion of Meselson and Stahl's experiment if, after the first generation, they had found two bands of DNA?

**DNA Replication in Bacteria**

DNA replication has been well studied in bacteria primarily because of the small size of the genome and the mutants that are available. *E. coli* has 4.6 million base pairs (Mbp) in a single circular chromosome and all of it is replicated in approximately 42 minutes, starting from a single origin of replication and proceeding around the circle bidirectionally (i.e., in both directions). This means that approximately 1000 nucleotides are added per second. The process is quite rapid and occurs with few errors.

DNA replication uses a large number of proteins and enzymes (Table 11.1). One of the key players is the enzyme **DNA polymerase**, also known as DNA pol. In bacteria, three main types of DNA polymerases are known: DNA pol I, DNA pol II, and DNA pol III. It is now known that DNA pol III is the enzyme required for DNA synthesis; DNA pol I and DNA pol II are primarily required for repair. DNA pol III adds deoxyribonucleotides each complementary to a nucleotide on the template strand, one by one to the 3'-OH group of the growing DNA chain. The addition of these
nucleotides requires energy. This energy is present in the bonds of three phosphate groups attached to each nucleotide (a triphosphate nucleotide), similar to how energy is stored in the phosphate bonds of adenosine triphosphate (ATP) (Figure 11.6). When the bond between the phosphates is broken and diphosphate is released, the energy released allows for the formation of a covalent phosphodiester bond by dehydration synthesis between the incoming nucleotide and the free 3’-OH group on the growing DNA strand.

![Figure 11.6](image)

Figure 11.6 This structure shows the guanosine triphosphate deoxyribonucleotide that is incorporated into a growing DNA strand by cleaving the two end phosphate groups from the molecule and transferring the energy to the sugar phosphate bond. The other three nucleotides form analogous structures.

**Initiation**

The initiation of replication occurs at specific nucleotide sequence called the origin of replication, where various proteins bind to begin the replication process. *E. coli* has a single origin of replication (as do most prokaryotes), called oriC, on its one chromosome. The origin of replication is approximately 245 base pairs long and is rich in adenine-thymine (AT) sequences.

Some of the proteins that bind to the origin of replication are important in making single-stranded regions of DNA accessible for replication. Chromosomal DNA is typically wrapped around histones (in eukaryotes and archaea) or histone-like proteins (in bacteria), and is supercoiled, or extensively wrapped and twisted on itself. This packaging makes the information in the DNA molecule inaccessible. However, enzymes called topoisomerases change the shape and supercoiling of the chromosome. For bacterial DNA replication to begin, the supercoiled chromosome is relaxed by topoisomerase II, also called DNA gyrase. An enzyme called helicase then separates the DNA strands by breaking the hydrogen bonds between the nitrogenous base pairs. Recall that AT sequences have fewer hydrogen bonds and, hence, have weaker interactions than guanine-cytosine (GC) sequences. These enzymes require ATP hydrolysis. As the DNA opens up, Y-shaped structures called replication forks are formed. Two replication forks are formed at the origin of replication, allowing for bidirectional replication and formation of a structure that looks like a bubble when viewed with a transmission electron microscope; as a result, this structure is called a replication bubble. The DNA near each replication fork is coated with single-stranded binding proteins to prevent the single-stranded DNA from rewinding into a double helix.

Once single-stranded DNA is accessible at the origin of replication, DNA replication can begin. However, DNA pol III is able to add nucleotides only in the 5’ to 3’ direction (a new DNA strand can be only extended in this direction). This is because DNA polymerase requires a free 3’-OH group to which it can add nucleotides by forming a covalent phosphodiester bond between the 3’-OH end and the 5’ phosphate of the next nucleotide. This also means that it cannot add nucleotides if a free 3’-OH group is not available, which is the case for a single strand of DNA. The problem is solved with the help of an RNA sequence that provides the free 3’-OH end. Because this sequence allows the start of DNA synthesis, it is appropriately called the primer. The primer is five to 10 nucleotides long and complementary to the parental or template DNA. It is synthesized by RNA primase, which is an RNA polymerase. Unlike DNA polymerases, RNA polymerases do not need a free 3’-OH group to synthesize an RNA molecule. Now that the primer provides the free 3’-OH group, DNA polymerase III can now extend this RNA primer, adding DNA nucleotides one by one that are complementary to the template strand (Figure 11.4).

**Elongation**

During elongation in DNA replication, the addition of nucleotides occurs at its maximal rate of about 1000 nucleotides per second. DNA polymerase III can only extend in the 5’ to 3’ direction, which poses a problem at
the replication fork. The DNA double helix is antiparallel; that is, one strand is oriented in the 5’ to 3’ direction and the other is oriented in the 3’ to 5’ direction (see Structure and Function of DNA). During replication, one strand, which is complementary to the 3’ to 5’ parental DNA strand, is synthesized continuously toward the replication fork because polymerase can add nucleotides in this direction. This continuously synthesized strand is known as the leading strand. The other strand, complementary to the 5’ to 3’ parental DNA, grows away from the replication fork, so the polymerase must move back toward the replication fork to begin adding bases to a new primer, again in the direction away from the replication fork. It does so until it bumps into the previously synthesized strand and then it moves back again (Figure 11.7). These steps produce small DNA sequence fragments known as Okazaki fragments, each separated by RNA primer. Okazaki fragments are named after the Japanese research team and married couple Reiji and Tsuneko Okazaki, who first discovered them in 1966. The strand with the Okazaki fragments is known as the lagging strand, and its synthesis is said to be discontinuous.

The leading strand can be extended from one primer alone, whereas the lagging strand needs a new primer for each of the short Okazaki fragments. The overall direction of the lagging strand will be 3’ to 5’, and that of the leading strand 5’ to 3’. A protein called the sliding clamp holds the DNA polymerase in place as it continues to add nucleotides. The sliding clamp is a ring-shaped protein that binds to the DNA and holds the polymerase in place. Beyond its role in initiation, topoisomerase also prevents the overwinding of the DNA double helix ahead of the replication fork as the DNA is opening up; it does so by causing temporary nicks in the DNA helix and then resealing it. As synthesis proceeds, the RNA primers are replaced by DNA. The primers are removed by the exonuclease activity of DNA polymerase I, and the gaps are filled in. The nicks that remain between the newly synthesized DNA (that replaced the RNA primer) and the previously synthesized DNA are sealed by the enzyme DNA ligase that catalyzes the formation of covalent phosphodiester linkage between the 3’-OH end of one DNA fragment and the 5’ phosphate end of the other fragment, stabilizing the sugar-phosphate backbone of the DNA molecule.
Figure 11.7  At the origin of replication, topoisomerase II relaxes the supercoiled chromosome. Two replication forks are formed by the opening of the double-stranded DNA at the origin, and helicase separates the DNA strands, which are coated by single-stranded binding proteins to keep the strands separated. DNA replication occurs in both directions. An RNA primer complementary to the parental strand is synthesized by RNA primase and is elongated by DNA polymerase III through the addition of nucleotides to the 3'-OH end. On the leading strand, DNA is synthesized continuously, whereas on the lagging strand, DNA is synthesized in short stretches called Okazaki fragments. RNA primers within the lagging strand are removed by the exonuclease activity of DNA polymerase I, and the Okazaki fragments are joined by DNA ligase.

Termination

Once the complete chromosome has been replicated, termination of DNA replication must occur. Although much is known about initiation of replication, less is known about the termination process. Following replication, the resulting complete circular genomes of prokaryotes are concatenated, meaning that the circular DNA chromosomes are interlocked and must be separated from each other. This is accomplished through the activity of bacterial topoisomerase IV, which introduces double-stranded breaks into DNA molecules, allowing them to separate from each other; the enzyme then reseals the circular chromosomes. The resolution of concatemers is an issue unique to prokaryotic DNA replication because of their circular chromosomes. Because both bacterial DNA gyrase and topoisomerase IV are distinct from their eukaryotic counterparts, these enzymes serve as targets for a class of antimicrobial drugs called quinolones.
The Molecular Machinery Involved in Bacterial DNA Replication

<table>
<thead>
<tr>
<th>Enzyme or Factor</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>DNA pol I</td>
<td>Exonuclease activity removes RNA primer and replaces it with newly synthesized DNA</td>
</tr>
<tr>
<td>DNA pol III</td>
<td>Main enzyme that adds nucleotides in the 5’ to 3’ direction</td>
</tr>
<tr>
<td>Helicase</td>
<td>Opens the DNA helix by breaking hydrogen bonds between the nitrogenous bases</td>
</tr>
<tr>
<td>Ligase</td>
<td>Seals the gaps between the Okazaki fragments on the lagging strand to create one continuous DNA strand</td>
</tr>
<tr>
<td>Primase</td>
<td>Synthesizes RNA primers needed to start replication</td>
</tr>
<tr>
<td>Single-stranded binding proteins</td>
<td>Bind to single-stranded DNA to prevent hydrogen bonding between DNA strands, reforming double-stranded DNA</td>
</tr>
<tr>
<td>Sliding clamp</td>
<td>Helps hold DNA pol III in place when nucleotides are being added</td>
</tr>
<tr>
<td>Topoisomerase II (DNA gyrase)</td>
<td>Relaxes supercoiled chromosome to make DNA more accessible for the initiation of replication; helps relieve the stress on DNA when unwinding, by causing breaks and then resealing the DNA</td>
</tr>
<tr>
<td>Topoisomerase IV</td>
<td>Introduces single-stranded break into concatenated chromosomes to release them from each other, and then reseals the DNA</td>
</tr>
</tbody>
</table>

Table 11.1

Check Your Understanding

- Which enzyme breaks the hydrogen bonds holding the two strands of DNA together so that replication can occur?
- Is it the lagging strand or the leading strand that is synthesized in the direction toward the opening of the replication fork?
- Which enzyme is responsible for removing the RNA primers in newly replicated bacterial DNA?

DNA Replication in Eukaryotes

Eukaryotic genomes are much more complex and larger than prokaryotic genomes and are typically composed of multiple linear chromosomes (Table 11.2). The human genome, for example, has 3 billion base pairs per haploid set of chromosomes, and 6 billion base pairs are inserted during replication. There are multiple origins of replication on each eukaryotic chromosome (Figure 11.8); the human genome has 30,000 to 50,000 origins of replication. The rate of replication is approximately 100 nucleotides per second—10 times slower than prokaryotic replication.
The essential steps of replication in eukaryotes are the same as in prokaryotes. Before replication can start, the DNA has to be made available as a template. Eukaryotic DNA is highly supercoiled and packaged, which is facilitated by many proteins, including histones (see *Structure and Function of Cellular Genomes*). At the origin of replication, a prereplication complex composed of several proteins, including helicase, forms and recruits other enzymes involved in the initiation of replication, including topoisomerase to relax supercoiling, single-stranded binding protein, RNA primase, and DNA polymerase. Following initiation of replication, in a process similar to that found in prokaryotes, elongation is facilitated by eukaryotic DNA polymerases. The leading strand is continuously synthesized by the eukaryotic polymerase enzyme pol δ, while the lagging strand is synthesized by pol ε. A sliding clamp protein holds the DNA polymerase in place so that it does not fall off the DNA. The enzyme ribonuclease H (RNase H), instead of a DNA polymerase as in bacteria, removes the RNA primer, which is then replaced with DNA nucleotides. The gaps that remain are sealed by DNA ligase.

Because eukaryotic chromosomes are linear, one might expect that their replication would be more straightforward. As in prokaryotes, the eukaryotic DNA polymerase can add nucleotides only in the 5’ to 3’ direction. In the leading strand, synthesis continues until it reaches either the end of the chromosome or another replication fork progressing in the opposite direction. On the lagging strand, DNA is synthesized in short stretches, each of which is initiated by a separate primer. When the replication fork reaches the end of the linear chromosome, there is no place to make a primer for the DNA fragment to be copied at the end of the chromosome. These ends thus remain unpaired and, over time, they may get progressively shorter as cells continue to divide.

The ends of the linear chromosomes are known as telomeres and consist of noncoding repetitive sequences. The telomeres protect coding sequences from being lost as cells continue to divide. In humans, a six base-pair sequence, TTAGGG, is repeated 100 to 1000 times to form the telomere. The discovery of the enzyme telomerase (Figure 11.9) clarified our understanding of how chromosome ends are maintained. Telomerase contains a catalytic part and a built-in RNA template. It attaches to the end of the chromosome, and complementary bases to the RNA template are added on the 3’ end of the DNA strand. Once the 3’ end of the lagging strand template is sufficiently elongated, DNA polymerase can add the nucleotides complementary to the ends of the chromosomes. In this way, the ends of the chromosomes are replicated. In humans, telomerase is typically active in germ cells and adult stem cells; it is not active in adult somatic cells and may be associated with the aging of these cells. Eukaryotic microbes including fungi and protozoans also produce telomerase to maintain chromosomal integrity. For her discovery of telomerase and its action, Elizabeth Blackburn (1948–) received the Nobel Prize for Medicine or Physiology in 2009.
In eukaryotes, the ends of the linear chromosomes are maintained by the action of the telomerase enzyme.

**Comparison of Bacterial and Eukaryotic Replication**

<table>
<thead>
<tr>
<th>Property</th>
<th>Bacteria</th>
<th>Eukaryotes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genome structure</td>
<td>Single circular chromosome</td>
<td>Multiple linear chromosomes</td>
</tr>
<tr>
<td>Number of origins per chromosome</td>
<td>Single</td>
<td>Multiple</td>
</tr>
<tr>
<td>Rate of replication</td>
<td>1000 nucleotides per second</td>
<td>100 nucleotides per second</td>
</tr>
<tr>
<td>Telomerase</td>
<td>Not present</td>
<td>Present</td>
</tr>
<tr>
<td>RNA primer removal</td>
<td>DNA pol I</td>
<td>RNase H</td>
</tr>
<tr>
<td>Strand elongation</td>
<td>DNA pol III</td>
<td>pol δ, pol ε</td>
</tr>
</tbody>
</table>

*Figure 11.9* In eukaryotes, the ends of the linear chromosomes are maintained by the action of the telomerase enzyme.

*Table 11.2*
This animation illustrates the process of DNA replication.

### Check Your Understanding

- How does the origin of replication differ between eukaryotes and prokaryotes?
- What polymerase enzymes are responsible for DNA synthesis during eukaryotic replication?
- What is found at the ends of the chromosomes in eukaryotes and why?

### DNA Replication of Extrachromosomal Elements: Plasmids and Viruses

To copy their nucleic acids, plasmids and viruses frequently use variations on the pattern of DNA replication described for prokaryote genomes. For more information on the wide range of viral replication strategies, see The Viral Life Cycle.

### Rolling Circle Replication

Whereas many bacterial plasmids (see Unique Characteristics of Prokaryotic Cells) replicate by a process similar to that used to copy the bacterial chromosome, other plasmids, several bacteriophages, and some viruses of eukaryotes use rolling circle replication (Figure 11.10). The circular nature of plasmids and the circularization of some viral genomes on infection make this possible. Rolling circle replication begins with the enzymatic nicking of one strand of the double-stranded circular molecule at the double-stranded origin (dso) site. In bacteria, DNA polymerase III binds to the 3’-OH group of the nicked strand and begins to unidirectionally replicate the DNA using the un-nicked strand as a template, displacing the nicked strand as it does so. Completion of DNA replication at the site of the original nick results in full displacement of the nicked strand, which may then recircularize into a single-stranded DNA molecule. RNA primase then synthesizes a primer to initiate DNA replication at the single-stranded origin (sso) site of the single-stranded DNA (ssDNA) molecule, resulting in a double-stranded DNA (dsDNA) molecule identical to the other circular DNA molecule.
11.3 RNA Transcription

Learning Objectives

- Explain how RNA is synthesized using DNA as a template
- Distinguish between transcription in prokaryotes and eukaryotes

During the process of transcription, the information encoded within the DNA sequence of one or more genes is transcribed into a strand of RNA, also called an RNA transcript. The resulting single-stranded RNA molecule, composed of ribonucleotides containing the bases adenine (A), cytosine (C), guanine (G), and uracil (U), acts as a mobile molecular copy of the original DNA sequence. Transcription in prokaryotes and in eukaryotes requires the DNA double helix to partially unwind in the region of RNA synthesis. The unwound region is called a transcription bubble. Transcription of a particular gene always proceeds from one of the two DNA strands that acts as a template, the so-called antisense strand. The RNA product is complementary to the template strand of DNA and is almost identical to the nontemplate DNA strand, or the sense strand. The only difference is that in RNA, all of the T nucleotides are replaced with U nucleotides; during RNA synthesis, U is incorporated when there is an A in the complementary antisense strand.

Transcription in Bacteria

Bacteria use the same RNA polymerase to transcribe all of their genes. Like DNA polymerase, RNA polymerase adds nucleotides one by one to the 3′-OH group of the growing nucleotide chain. One critical difference in activity between DNA polymerase and RNA polymerase is the requirement for a 3′-OH onto which to add nucleotides: DNA polymerase requires such a 3′-OH group, thus necessitating a primer, whereas RNA polymerase does not. During
transcription, a ribonucleotide complementary to the DNA template strand is added to the growing RNA strand and a covalent phosphodiester bond is formed by dehydration synthesis between the new nucleotide and the last one added. In *E. coli*, RNA polymerase comprises six polypeptide subunits, five of which compose the polymerase core enzyme responsible for adding RNA nucleotides to a growing strand. The sixth subunit is known as sigma (σ). The σ factor enables RNA polymerase to bind to a specific promoter, thus allowing for the transcription of various genes. There are various σ factors that allow for transcription of various genes.

**Initiation**

The **initiation of transcription** begins at a **promoter**, a DNA sequence onto which the transcription machinery binds and initiates transcription. The nucleotide pair in the DNA double helix that corresponds to the site from which the first 5’ RNA nucleotide is transcribed is the initiation site. Nucleotides preceding the initiation site are designated “upstream,” whereas nucleotides following the initiation site are called “downstream” nucleotides. In most cases, promoters are located just upstream of the genes they regulate. Although promoter sequences vary among bacterial genomes, a few elements are conserved. At the –10 and –35 positions within the DNA prior to the initiation site (designated +1), there are two promoter consensus sequences, or regions that are similar across all promoters and across various bacterial species. The –10 consensus sequence, called the TATA box, is TATAAT. The –35 sequence is recognized and bound by σ.

**Elongation**

The **elongation in transcription** phase begins when the σ subunit dissociates from the polymerase, allowing the core enzyme to synthesize RNA complementary to the DNA template in a 5’ to 3’ direction at a rate of approximately 40 nucleotides per second. As elongation proceeds, the DNA is continuously unwound ahead of the core enzyme and rewound behind it (Figure 11.11).

![Figure 11.11](image_url) During elongation, the bacterial RNA polymerase tracks along the DNA template, synthesizes mRNA in the 5’ to 3’ direction, and unwinds and rewinds the DNA as it is read.

**Termination**

Once a gene is transcribed, the bacterial polymerase must dissociate from the DNA template and liberate the newly made RNA. This is referred to as **termination of transcription**. The DNA template includes repeated nucleotide sequences that act as termination signals, causing RNA polymerase to stall and release from the DNA template, freeing the RNA transcript.
Check Your Understanding

• Where does σ factor of RNA polymerase bind DNA to start transcription?
• What occurs to initiate the polymerization activity of RNA polymerase?
• Where does the signal to end transcription come from?

Transcription in Eukaryotes

Prokaryotes and eukaryotes perform fundamentally the same process of transcription, with a few significant differences (see Table 11.3). Eukaryotes use three different polymerases, RNA polymerases I, II, and III, all structurally distinct from the bacterial RNA polymerase. Each transcribes a different subset of genes. Interestingly, archaea contain a single RNA polymerase that is more closely related to eukaryotic RNA polymerase II than to its bacterial counterpart. Eukaryotic mRNAs are also usually monocistronic, meaning that they each encode only a single polypeptide, whereas prokaryotic mRNAs of bacteria and archaea are commonly polycistronic, meaning that they encode multiple polypeptides.

The most important difference between prokaryotes and eukaryotes is the latter’s membrane-bound nucleus, which influences the ease of use of RNA molecules for protein synthesis. With the genes bound in a nucleus, the eukaryotic cell must transport protein-encoding RNA molecules to the cytoplasm to be translated. Protein-encoding primary transcripts, the RNA molecules directly synthesized by RNA polymerase, must undergo several processing steps to protect these RNA molecules from degradation during the time they are transferred from the nucleus to the cytoplasm and translated into a protein. For example, eukaryotic mRNAs may last for several hours, whereas the typical prokaryotic mRNA lasts no more than 5 seconds.

The primary transcript (also called pre-mRNA) is first coated with RNA-stabilizing proteins to protect it from degradation while it is processed and exported out of the nucleus. The first type of processing begins while the primary transcript is still being synthesized; a special 7-methylguanosine nucleotide, called the 5’ cap, is added to the 5’ end of the growing transcript. In addition to preventing degradation, factors involved in subsequent protein synthesis recognize the cap, which helps initiate translation by ribosomes. Once elongation is complete, another processing enzyme then adds a string of approximately 200 adenine nucleotides to the 3’ end, called the poly-A tail. This modification further protects the pre-mRNA from degradation and signals to cellular factors that the transcript needs to be exported to the cytoplasm.

Eukaryotic genes that encode polypeptides are composed of coding sequences called exons (ex-on signifies that they are expressed) and intervening sequences called introns (int-ron denotes their intervening role). Transcribed RNA sequences corresponding to introns do not encode regions of the functional polypeptide and are removed from the pre-mRNA during processing. It is essential that all of the intron-encoded RNA sequences are completely and precisely removed from a pre-mRNA before protein synthesis so that the exon-encoded RNA sequences are properly joined together to code for a functional polypeptide. If the process errs by even a single nucleotide, the sequences of the rejoined exons would be shifted, and the resulting polypeptide would be nonfunctional. The process of removing intron-encoded RNA sequences and reconnecting those encoded by exons is called RNA splicing and is facilitated by the action of a spliceosome containing small nuclear ribonucleoproteins (snRNPs). Intron-encoded RNA sequences are removed from the pre-mRNA while it is still in the nucleus. Although they are not translated, introns appear to have various functions, including gene regulation and mRNA transport. On completion of these modifications, the mature transcript, the mRNA that encodes a polypeptide, is transported out of the nucleus, destined for the cytoplasm for translation. Introns can be spliced out differently, resulting in various exons being included or excluded from the final mRNA product. This process is known as alternative splicing. The advantage of alternative splicing is that different types of mRNA transcripts can be generated, all derived from the same DNA sequence. In recent years, it has been shown that some archaea also have the ability to splice their pre-mRNA.
Comparison of Transcription in Bacteria Versus Eukaryotes

<table>
<thead>
<tr>
<th>Property</th>
<th>Bacteria</th>
<th>Eukaryotes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of polypeptides encoded per mRNA</td>
<td>Monocistronic or polycistronic</td>
<td>Exclusively monocistronic</td>
</tr>
<tr>
<td>Strand elongation</td>
<td>core + σ = holoenzyme</td>
<td>RNA polymerases I, II, or III</td>
</tr>
<tr>
<td>Addition of 5’ cap</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Addition of 3’ poly-A tail</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Splicing of pre-mRNA</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Table 11.3

Link to Learning

Visualize how mRNA splicing (https://openstax.org/l/22mrnasplice) happens by watching the process in action in this video. See how introns are removed during RNA splicing (https://openstax.org/l/22rnasplice) here.

Check Your Understanding

- In eukaryotic cells, how is the RNA transcript from a gene for a protein modified after it is transcribed?
- Do exons or introns contain information for protein sequences?

Clinical Focus

Part 2

In the emergency department, a nurse told Mark that he had made a good decision to come to the hospital because his symptoms indicated an infection that had gotten out of control. Mark’s symptoms had progressed, with the area of skin affected and the amount of swelling increasing. Within the affected area, a rash had begun, blistering and small gas pockets underneath the outermost layer of skin had formed, and some of the skin was becoming gray. Based on the putrid smell of the pus draining from one of the blisters, the rapid progression of the infection, and the visual appearance of the affected skin, the physician immediately began treatment for necrotizing fasciitis. Mark’s physician ordered a culture of the fluid draining from the blister and also ordered blood work, including a white blood cell count.

Mark was admitted to the intensive care unit and began intravenous administration of a broad-spectrum antibiotic to try to minimize further spread of the infection. Despite antibiotic therapy, Mark’s condition deteriorated quickly. Mark became confused and dizzy. Within a few hours of his hospital admission, his blood pressure dropped significantly and his breathing became shallower and more rapid. Additionally, blistering increased, with the blisters intensifying in color to purplish black, and the wound itself seemed to be progressing rapidly up Mark’s leg.

- What are possible causative agents of Mark’s necrotizing fasciitis?
11.4 Protein Synthesis (Translation)

Learning Objectives
- Describe the genetic code and explain why it is considered almost universal
- Explain the process of translation and the functions of the molecular machinery of translation
- Compare translation in eukaryotes and prokaryotes

The synthesis of proteins consumes more of a cell’s energy than any other metabolic process. In turn, proteins account for more mass than any other macromolecule of living organisms. They perform virtually every function of a cell, serving as both functional (e.g., enzymes) and structural elements. The process of translation, or protein synthesis, the second part of gene expression, involves the decoding by a ribosome of an mRNA message into a polypeptide product.

The Genetic Code
Translation of the mRNA template converts nucleotide-based genetic information into the “language” of amino acids to create a protein product. A protein sequence consists of 20 commonly occurring amino acids. Each amino acid is defined within the mRNA by a triplet of nucleotides called a codon. The relationship between an mRNA codon and its corresponding amino acid is called the genetic code.

The three-nucleotide code means that there is a total of 64 possible combinations (4^3, with four different nucleotides possible at each of the three different positions within the codon). This number is greater than the number of amino acids and a given amino acid is encoded by more than one codon (Figure 11.12). This redundancy in the genetic code is called degeneracy. Typically, whereas the first two positions in a codon are important for determining which amino acid will be incorporated into a growing polypeptide, the third position, called the wobble position, is less critical. In some cases, if the nucleotide in the third position is changed, the same amino acid is still incorporated.

Whereas 61 of the 64 possible triplets code for amino acids, three of the 64 codons do not code for an amino acid; they terminate protein synthesis, releasing the polypeptide from the translation machinery. These are called stop codons or nonsense codons. Another codon, AUG, also has a special function. In addition to specifying the amino acid methionine, it also typically serves as the start codon to initiate translation. The reading frame, the way nucleotides in mRNA are grouped into codons, for translation is set by the AUG start codon near the 5’ end of the mRNA. Each set of three nucleotides following this start codon is a codon in the mRNA message.

The genetic code is nearly universal. With a few exceptions, virtually all species use the same genetic code for protein synthesis, which is powerful evidence that all extant life on earth shares a common origin. However, unusual amino acids such as selenocysteine and pyrrolysine have been observed in archaea and bacteria. In the case of selenocysteine, the codon used is UGA (normally a stop codon). However, UGA can encode for selenocysteine using a stem-loop structure (known as the selenocysteine insertion sequence, or SECIS element), which is found at the 3’ untranslated region of the mRNA. Pyrrolysine uses a different stop codon, UAG. The incorporation of pyrrolysine requires the pylS gene and a unique transfer RNA (tRNA) with a CUA anticodon.
This figure shows the genetic code for translating each nucleotide triplet in mRNA into an amino acid or a termination signal in a nascent protein. The first letter of a codon is shown vertically on the left, the second letter of a codon is shown horizontally across the top, and the third letter of a codon is shown vertically on the right. (credit: modification of work by National Institutes of Health)

**Check Your Understanding**

- How many bases are in each codon?
- What amino acid is coded for by the codon AAU?
- What happens when a stop codon is reached?

**The Protein Synthesis Machinery**

In addition to the mRNA template, many molecules and macromolecules contribute to the process of translation. The composition of each component varies across taxa; for instance, ribosomes may consist of different numbers of ribosomal RNAs (rRNAs) and polypeptides depending on the organism. However, the general structures and functions of the protein synthesis machinery are comparable from bacteria to human cells. Translation requires the input of an mRNA template, ribosomes, tRNAs, and various enzymatic factors.

**Ribosomes**

A ribosome is a complex macromolecule composed of catalytic rRNAs (called ribozymes) and structural rRNAs, as well as many distinct polypeptides. Mature rRNAs make up approximately 50% of each ribosome. Prokaryotes have 70S ribosomes, whereas eukaryotes have 80S ribosomes in the cytoplasm and rough endoplasmic reticulum, and 70S ribosomes in mitochondria and chloroplasts. Ribosomes dissociate into large and small subunits when they are not synthesizing proteins and reassociate during the initiation of translation. In *E. coli*, the small subunit is described as 30S (which contains the 16S rRNA subunit), and the large subunit is 50S (which contains the 5S and 23S rRNA subunits), for a total of 70S (Svedberg units are not additive). Eukaryote ribosomes have a small 40S subunit (which contains the 18S rRNA subunit) and a large 60S subunit (which contains the 5S, 5.8S and 28S rRNA subunits), for a
total of 80S. The small subunit is responsible for binding the mRNA template, whereas the large subunit binds tRNAs (discussed in the next subsection).

Each mRNA molecule is simultaneously translated by many ribosomes, all synthesizing protein in the same direction: reading the mRNA from 5’ to 3’ and synthesizing the polypeptide from the N terminus to the C terminus. The complete structure containing an mRNA with multiple associated ribosomes is called a polyribosome (or polysome). In both bacteria and archaea, before transcriptional termination occurs, each protein-encoding transcript is already being used to begin synthesis of numerous copies of the encoded polypeptide(s) because the processes of transcription and translation can occur concurrently, forming polyribosomes (Figure 11.13). The reason why transcription and translation can occur simultaneously is because both of these processes occur in the same 5’ to 3’ direction, they both occur in the cytoplasm of the cell, and because the RNA transcript is not processed once it is transcribed. This allows a prokaryotic cell to respond to an environmental signal requiring new proteins very quickly. In contrast, in eukaryotic cells, simultaneous transcription and translation is not possible. Although polyribosomes also form in eukaryotes, they cannot do so until RNA synthesis is complete and the RNA molecule has been modified and transported out of the nucleus.

Transfer RNAs (tRNAs) are structural RNA molecules and, depending on the species, many different types of tRNAs exist in the cytoplasm. Bacterial species typically have between 60 and 90 types. Serving as adaptors, each tRNA type binds to a specific codon on the mRNA template and adds the corresponding amino acid to the polypeptide chain. Therefore, tRNAs are the molecules that actually “translate” the language of RNA into the language of proteins. As the adaptor molecules of translation, it is surprising that tRNAs can fit so much specificity into such a small package. The tRNA molecule interacts with three factors: aminoacyl tRNA synthetases, ribosomes, and mRNA.

Mature tRNAs take on a three-dimensional structure when complementary bases exposed in the single-stranded RNA molecule hydrogen bond with each other (Figure 11.14). This shape positions the amino-acid binding site, called the CCA amino acid binding end, which is a cytosine-cytosine-adenine sequence at the 3’ end of the tRNA, and the anticodon at the other end. The anticodon is a three-nucleotide sequence that bonds with an mRNA codon through complementary base pairing.

An amino acid is added to the end of a tRNA molecule through the process of tRNA “charging,” during which each tRNA molecule is linked to its correct or cognate amino acid by a group of enzymes called aminoacyl tRNA synthetases. At least one type of aminoacyl tRNA synthetase exists for each of the 20 amino acids. During this process, the amino acid is first activated by the addition of adenosine monophosphate (AMP) and then transferred to the tRNA, making it a charged tRNA, and AMP is released.
Describe the structure and composition of the prokaryotic ribosome.

In what direction is the mRNA template read?

Describe the structure and function of a tRNA.

The Mechanism of Protein Synthesis

Translation is similar in prokaryotes and eukaryotes. Here we will explore how translation occurs in *E. coli*, a representative prokaryote, and specify any differences between bacterial and eukaryotic translation.

Initiation

The initiation of protein synthesis begins with the formation of an initiation complex. In *E. coli*, this complex involves the small 30S ribosome, the mRNA template, three initiation factors that help the ribosome assemble correctly, guanosine triphosphate (GTP) that acts as an energy source, and a special initiator tRNA carrying N-formyl-methionine (fMet-tRNAfMet) (Figure 11.15). The initiator tRNA interacts with the start codon AUG of the mRNA and carries a formylated methionine (fMet). Because of its involvement in initiation, fMet is inserted at the beginning (N terminus) of every polypeptide chain synthesized by *E. coli*. In *E. coli* mRNA, a leader sequence upstream of the first AUG codon, called the Shine-Dalgarno sequence (also known as the ribosomal binding site AGGAGG), interacts through complementary base pairing with the rRNA molecules that compose the ribosome. This interaction anchors the 30S ribosomal subunit at the correct location on the mRNA template. At this point, the 50S ribosomal subunit then binds to the initiation complex, forming an intact ribosome.
In eukaryotes, initiation complex formation is similar, with the following differences:

- The initiator tRNA is a different specialized tRNA carrying methionine, called Met-tRNAi.
- Instead of binding to the mRNA at the Shine-Dalgarno sequence, the eukaryotic initiation complex recognizes the 5’ cap of the eukaryotic mRNA, then tracks along the mRNA in the 5’ to 3’ direction until the AUG start codon is recognized. At this point, the 60S subunit binds to the complex of Met-tRNAi, mRNA, and the 40S subunit.

Elongation

In prokaryotes and eukaryotes, the basics of elongation of translation are the same. In E. coli, the binding of the 50S ribosomal subunit to produce the intact ribosome forms three functionally important ribosomal sites: The A (aminoacyl) site binds incoming charged aminoacyl tRNAs. The P (peptidyl) site binds charged tRNAs carrying amino acids that have formed peptide bonds with the growing polypeptide chain but have not yet dissociated from their corresponding tRNA. The E (exit) site releases dissociated tRNAs so that they can be recharged with free amino acids. There is one notable exception to this assembly line of tRNAs: During initiation complex formation, bacterial fMet-tRNAfMet or eukaryotic Met-tRNAi enters the P site directly without first entering the A site, providing a free A site ready to accept the tRNA corresponding to the first codon after the AUG.

Elongation proceeds with single-codon movements of the ribosome each called a translocation event. During each translocation event, the charged tRNAs enter at the A site, then shift to the P site, and then finally to the E site for removal. Ribosomal movements, or steps, are induced by conformational changes that advance the ribosome by three
bases in the 3' direction. Peptide bonds form between the amino group of the amino acid attached to the A-site tRNA and the carboxyl group of the amino acid attached to the P-site tRNA. The formation of each peptide bond is catalyzed by peptidyl transferase, an RNA-based ribozyme that is integrated into the 50S ribosomal subunit. The amino acid bound to the P-site tRNA is also linked to the growing polypeptide chain. As the ribosome steps across the mRNA, the former P-site tRNA enters the E site, detaches from the amino acid, and is expelled. Several of the steps during elongation, including binding of a charged aminoacyl tRNA to the A site and translocation, require energy derived from GTP hydrolysis, which is catalyzed by specific elongation factors. Amazingly, the E. coli translation apparatus takes only 0.05 seconds to add each amino acid, meaning that a 200 amino-acid protein can be translated in just 10 seconds.

**Termination**

The termination of translation occurs when a nonsense codon (UAA, UAG, or UGA) is encountered for which there is no complementary tRNA. On aligning with the A site, these nonsense codons are recognized by release factors in prokaryotes and eukaryotes that result in the P-site amino acid detaching from its tRNA, releasing the newly made polypeptide. The small and large ribosomal subunits dissociate from the mRNA and from each other; they are recruited almost immediately into another translation initiation complex.

In summary, there are several key features that distinguish prokaryotic gene expression from that seen in eukaryotes. These are illustrated in Figure 11.16 and listed in Figure 11.17.

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**Figure 11.16**  (a) In prokaryotes, the processes of transcription and translation occur simultaneously in the cytoplasm, allowing for a rapid cellular response to an environmental cue. (b) In eukaryotes, transcription is localized to the nucleus and translation is localized to the cytoplasm, separating these processes and necessitating RNA processing for stability.
Protein Targeting, Folding, and Modification

During and after translation, polypeptides may need to be modified before they are biologically active. Post-translational modifications include:

1. removal of translated signal sequences—short tails of amino acids that aid in directing a protein to a specific cellular compartment
2. proper “folding” of the polypeptide and association of multiple polypeptide subunits, often facilitated by chaperone proteins, into a distinct three-dimensional structure
3. proteolytic processing of an inactive polypeptide to release an active protein component, and
4. various chemical modifications (e.g., phosphorylation, methylation, or glycosylation) of individual amino acids.
11.5 Mutations

Learning Objectives

- Compare point mutations and frameshift mutations
- Describe the differences between missense, nonsense, and silent mutations
- Describe the differences between light and dark repair
- Explain how different mutagens act
- Explain why the Ames test can be used to detect carcinogens
- Analyze sequences of DNA and identify examples of types of mutations

A mutation is a heritable change in the DNA sequence of an organism. The resulting organism, called a mutant, may have a recognizable change in phenotype compared to the wild type, which is the phenotype most commonly observed in nature. A change in the DNA sequence is conferred to mRNA through transcription, and may lead to an altered amino acid sequence in a protein on translation. Because proteins carry out the vast majority of cellular functions, a change in amino acid sequence in a protein may lead to an altered phenotype for the cell and organism.

Effects of Mutations on DNA Sequence

There are several types of mutations that are classified according to how the DNA molecule is altered. One type, called a point mutation, affects a single base and most commonly occurs when one base is substituted or replaced by another. Mutations also result from the addition of one or more bases, known as an insertion, or the removal of one or more bases, known as a deletion.

Effects of Mutations on Protein Structure and Function

Point mutations may have a wide range of effects on protein function (Figure 11.18). As a consequence of the degeneracy of the genetic code, a point mutation will commonly result in the same amino acid being incorporated into the resulting polypeptide despite the sequence change. This change would have no effect on the protein’s structure, and is thus called a silent mutation. A missense mutation results in a different amino acid being incorporated into the resulting polypeptide. The effect of a missense mutation depends on how chemically different the new amino acid is from the wild-type amino acid. The location of the changed amino acid within the protein also is important. For example, if the changed amino acid is part of the enzyme’s active site, then the effect of the missense mutation may be significant. Many missense mutations result in proteins that are still functional, at least to some degree. Sometimes the effects of missense mutations may be only apparent under certain environmental conditions; such missense mutations are called conditional mutations. Rarely, a missense mutation may be beneficial. Under the right environmental conditions, this type of mutation may give the organism that harbors it a selective advantage. Yet another type of point mutation, called a nonsense mutation, converts a codon encoding an amino acid (a sense codon) into a stop codon (a nonsense codon). Nonsense mutations result in the synthesis of proteins that are shorter than the wild type and typically not functional.

Deletions and insertions also cause various effects. Because codons are triplets of nucleotides, insertions or deletions in groups of three nucleotides may lead to the insertion or deletion of one or more amino acids and may not cause significant effects on the resulting protein’s functionality. However, frameshift mutations, caused by insertions or deletions of a number of nucleotides that are not a multiple of three are extremely problematic because a shift in the
reading frame results (Figure 11.18). Because ribosomes read the mRNA in triplet codons, frameshift mutations can change every amino acid after the point of the mutation. The new reading frame may also include a stop codon before the end of the coding sequence. Consequently, proteins made from genes containing frameshift mutations are nearly always nonfunctional.

![Diagram of point mutation, missense, nonsense, and frameshift mutation](image)

**Figure 11.18** Mutations can lead to changes in the protein sequence encoded by the DNA.

**Check Your Understanding**

- What are the reasons a nucleotide change in a gene for a protein might not have any effect on the phenotype of that gene?

- Is it possible for an insertion of three nucleotides together after the fifth nucleotide in a protein-coding gene to produce a protein that is shorter than normal? How or how not?
A Beneficial Mutation

Since the first case of infection with human immunodeficiency virus (HIV) was reported in 1981, nearly 40 million people have died from HIV infection, the virus that causes acquired immune deficiency syndrome (AIDS). The virus targets helper T cells that play a key role in bridging the innate and adaptive immune response, infecting and killing cells normally involved in the body’s response to infection. There is no cure for HIV infection, but many drugs have been developed to slow or block the progression of the virus. Although individuals around the world may be infected, the highest prevalence among people 15–49 years old is in sub-Saharan Africa, where nearly one person in 20 is infected, accounting for greater than 70% of the infections worldwide (Figure 11.19). Unfortunately, this is also a part of the world where prevention strategies and drugs to treat the infection are the most lacking.

In recent years, scientific interest has been piqued by the discovery of a few individuals from northern Europe who are resistant to HIV infection. In 1998, American geneticist Stephen J. O’Brien at the National Institutes of Health (NIH) and colleagues published the results of their genetic analysis of more than 4,000 individuals. These indicated that many individuals of Eurasian descent (up to 14% in some ethnic groups) have a deletion mutation, called CCR5-delta 32, in the gene encoding CCR5. CCR5 is a coreceptor found on the surface of T cells that is necessary for many strains of the virus to enter the host cell. The mutation leads to the production of a receptor to which HIV cannot effectively bind and thus blocks viral entry. People homozygous for this mutation have greatly reduced susceptibility to HIV infection, and those who are heterozygous have some protection from infection as well.

It is not clear why people of northern European descent, specifically, carry this mutation, but its prevalence seems to be highest in northern Europe and steadily decreases in populations as one moves south. Research indicates that the mutation has been present since before HIV appeared and may have been selected for in European populations as a result of exposure to the plague or smallpox. This mutation may protect individuals from plague (caused by the bacterium *Yersinia pestis*) and smallpox (caused by the variola virus) because this receptor may also be involved in these diseases. The age of this mutation is a matter of debate, but estimates suggest it appeared between 1875 years to 225 years ago, and may have been spread from Northern Europe through Viking invasions.

This exciting finding has led to new avenues in HIV research, including looking for drugs to block CCR5 binding to HIV in individuals who lack the mutation. Although DNA testing to determine which individuals carry the CCR5-delta 32 mutation is possible, there are documented cases of individuals homozygous for the mutation contracting HIV. For this reason, DNA testing for the mutation is not widely recommended by public health officials so as not to encourage risky behavior in those who carry the mutation. Nevertheless, inhibiting the binding of HIV to CCR5 continues to be a valid strategy for the development of drug therapies for those infected with HIV.

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Causes of Mutations

Mistakes in the process of DNA replication can cause spontaneous mutations to occur. The error rate of DNA polymerase is one incorrect base per billion base pairs replicated. Exposure to mutagens can cause induced mutations, which are various types of chemical agents or radiation (Table 11.4). Exposure to a mutagen can increase the rate of mutation more than 1000-fold. Mutagens are often also carcinogens, agents that cause cancer. However, whereas nearly all carcinogens are mutagenic, not all mutagens are necessarily carcinogens.

Chemical Mutagens

Various types of chemical mutagens interact directly with DNA either by acting as nucleoside analogs or by modifying nucleotide bases. Chemicals called nucleoside analogs are structurally similar to normal nucleotide bases and can be incorporated into DNA during replication (Figure 11.20). These base analogs induce mutations because they often have different base-pairing rules than the bases they replace. Other chemical mutagens can modify normal DNA bases, resulting in different base-pairing rules. For example, nitrous acid deaminates cytosine, converting it to uracil. Uracil then pairs with adenine in a subsequent round of replication, resulting in the conversion of a GC base pair to an AT base pair. Nitrous acid also deaminates adenine to hypoxanthine, which base pairs with cytosine instead of thymine, resulting in the conversion of a TA base pair to a CG base pair.

Chemical mutagens known as intercalating agents work differently. These molecules slide between the stacked nitrogenous bases of the DNA double helix, distorting the molecule and creating atypical spacing between nucleotide base pairs (Figure 11.21). As a result, during DNA replication, DNA polymerase may either skip replicating...
several nucleotides (creating a deletion) or insert extra nucleotides (creating an insertion). Either outcome may lead to a frameshift mutation. Combustion products like polycyclic aromatic hydrocarbons are particularly dangerous intercalating agents that can lead to mutation-caused cancers. The intercalating agents ethidium bromide and acridine orange are commonly used in the laboratory to stain DNA for visualization and are potential mutagens.

Figure 11.20  (a) 2-aminopurine nucleoside (2AP) structurally is a nucleoside analog to adenine nucleoside, whereas 5-bromouracil (5BU) is a nucleoside analog to thymine nucleoside. 2AP base pairs with C, converting an AT base pair to a GC base pair after several rounds of replication. 5BU pairs with G, converting an AT base pair to a GC base pair after several rounds of replication. (b) Nitrous acid is a different type of chemical mutagen that modifies already existing nucleoside bases like C to produce U, which base pairs with A. This chemical modification, as shown here, results in converting a CG base pair to a TA base pair.
Figure 11.21 Intercalating agents, such as acridine, introduce atypical spacing between base pairs, resulting in DNA polymerase introducing either a deletion or an insertion, leading to a potential frameshift mutation.

Radiation

Exposure to either ionizing or nonionizing radiation can each induce mutations in DNA, although by different mechanisms. Strong ionizing radiation like X-rays and gamma rays can cause single- and double-stranded breaks in the DNA backbone through the formation of hydroxyl radicals on radiation exposure (Figure 11.22). Ionizing radiation can also modify bases; for example, the deamination of cytosine to uracil, analogous to the action of nitrous acid. 

Ionizing radiation exposure is used to kill microbes to sterilize medical devices and foods, because of its dramatic nonspecific effect in damaging DNA, proteins, and other cellular components (see Using Physical Methods to Control Microorganisms).

Nonionizing radiation, like ultraviolet light, is not energetic enough to initiate these types of chemical changes. However, nonionizing radiation can induce dimer formation between two adjacent pyrimidine bases, commonly two thymines, within a nucleotide strand. During thymine dimer formation, the two adjacent thymines become covalently linked and, if left unrepaired, both DNA replication and transcription are stalled at this point. DNA polymerase may proceed and replicate the dimer incorrectly, potentially leading to frameshift or point mutations.

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Figure 11.22  (a) Ionizing radiation may lead to the formation of single-stranded and double-stranded breaks in the sugar-phosphate backbone of DNA, as well as to the modification of bases (not shown). (b) Nonionizing radiation like ultraviolet light can lead to the formation of thymine dimers, which can stall replication and transcription and introduce frameshift or point mutations.

A Summary of Mutagenic Agents

<table>
<thead>
<tr>
<th>Mutagenic Agents</th>
<th>Mode of Action</th>
<th>Effect on DNA</th>
<th>Resulting Type of Mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nucleoside analogs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-aminopurine</td>
<td>Is inserted in place of A but base pairs with C</td>
<td>Converts AT to GC base pair</td>
<td>Point</td>
</tr>
<tr>
<td>5-bromouracil</td>
<td>Is inserted in place of T but base pairs with G</td>
<td>Converts AT to GC base pair</td>
<td>Point</td>
</tr>
<tr>
<td>Nucleotide-modifying agent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nitrous oxide</td>
<td>Deaminates C to U</td>
<td>Converts GC to AT base pair</td>
<td>Point</td>
</tr>
<tr>
<td>Intercalating agents</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acridine orange, ethidium bromide, polycyclic aromatic hydrocarbons</td>
<td>Distorts double helix, creates unusual spacing between nucleotides</td>
<td>Introduces small deletions and insertions</td>
<td>Frameshift</td>
</tr>
<tr>
<td>Ionizing radiation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>X-rays, γ-rays</td>
<td>Forms hydroxyl radicals</td>
<td>Causes single- and double-strand DNA breaks</td>
<td>Repair mechanisms may introduce mutations</td>
</tr>
<tr>
<td>X-rays, γ-rays</td>
<td>Modifies bases (e.g., deaminating C to U)</td>
<td>Converts GC to AT base pair</td>
<td>Point</td>
</tr>
<tr>
<td>Nonionizing radiation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ultraviolet</td>
<td>Forms pyrimidine (usually thymine) dimers</td>
<td>Causes DNA replication errors</td>
<td>Frameshift or point</td>
</tr>
</tbody>
</table>

Table 11.4
Check Your Understanding

- How does a base analog introduce a mutation?
- How does an intercalating agent introduce a mutation?
- What type of mutagen causes thymine dimers?

DNA Repair

The process of DNA replication is highly accurate, but mistakes can occur spontaneously or be induced by mutagens. Uncorrected mistakes can lead to serious consequences for the phenotype. Cells have developed several repair mechanisms to minimize the number of mutations that persist.

Proofreading

Most of the mistakes introduced during DNA replication are promptly corrected by most DNA polymerases through a function called proofreading. In proofreading, the DNA polymerase reads the newly added base, ensuring that it is complementary to the corresponding base in the template strand before adding the next one. If an incorrect base has been added, the enzyme makes a cut to release the wrong nucleotide and a new base is added.

Mismatch Repair

Some errors introduced during replication are corrected shortly after the replication machinery has moved. This mechanism is called mismatch repair. The enzymes involved in this mechanism recognize the incorrectly added nucleotide, excise it, and replace it with the correct base. One example is the methyl-directed mismatch repair in *E. coli*. The DNA is hemimethylated. This means that the parental strand is methylated while the newly synthesized daughter strand is not. It takes several minutes before the new strand is methylated. Proteins MutS, MutL, and MutH bind to the hemimethylated site where the incorrect nucleotide is found. MutH cuts the nonmethylated strand (the new strand). An exonuclease removes a portion of the strand (including the incorrect nucleotide). The gap formed is then filled in by DNA pol III and ligase.

Repair of Thymine Dimers

Because the production of thymine dimers is common (many organisms cannot avoid ultraviolet light), mechanisms have evolved to repair these lesions. In nucleotide excision repair (also called dark repair), enzymes remove the pyrimidine dimer and replace it with the correct nucleotides (Figure 11.23). In *E. coli*, the DNA is scanned by an enzyme complex. If a distortion in the double helix is found that was introduced by the pyrimidine dimer, the enzyme complex cuts the sugar-phosphate backbone several bases upstream and downstream of the dimer, and the segment of DNA between these two cuts is then enzymatically removed. DNA pol I replaces the missing nucleotides with the correct ones and DNA ligase seals the gap in the sugar-phosphate backbone.

The direct repair (also called light repair) of thymine dimers occurs through the process of photoreactivation in the presence of visible light. An enzyme called photolyase recognizes the distortion in the DNA helix caused by the thymine dimer and binds to the dimer. Then, in the presence of visible light, the photolyase enzyme changes conformation and breaks apart the thymine dimer, allowing the thymines to again correctly base pair with the adenines on the complementary strand. Photoreactivation appears to be present in all organisms, with the exception of placental mammals, including humans. Photoreactivation is particularly important for organisms chronically exposed to ultraviolet radiation, like plants, photosynthetic bacteria, algae, and corals, to prevent the accumulation of mutations caused by thymine dimer formation.
Figure 11.23  Bacteria have two mechanisms for repairing thymine dimers. (a) In nucleotide excision repair, an enzyme complex recognizes the distortion in the DNA complex around the thymine dimer and cuts and removes the damaged DNA strand. The correct nucleotides are replaced by DNA pol I and the nucleotide strand is sealed by DNA ligase. (b) In photoreactivation, the enzyme photolyase binds to the thymine dimer and, in the presence of visible light, breaks apart the dimer, restoring the base pairing of the thymines with complementary adenines on the opposite DNA strand.
During mismatch repair, how does the enzyme recognize which is the new and which is the old strand?

How does an intercalating agent introduce a mutation?

What type of mutation does photolyase repair?

Identifying Bacterial Mutants

One common technique used to identify bacterial mutants is called replica plating. This technique is used to detect nutritional mutants, called auxotrophs, which have a mutation in a gene encoding an enzyme in the biosynthesis pathway of a specific nutrient, such as an amino acid. As a result, whereas wild-type cells retain the ability to grow normally on a medium lacking the specific nutrient, auxotrophs are unable to grow on such a medium. During replica plating (Figure 11.24), a population of bacterial cells is mutagenized and then plated as individual cells on a complex nutritionally complete plate and allowed to grow into colonies. Cells from these colonies are removed from this master plate, often using sterile velvet. This velvet, containing cells, is then pressed in the same orientation onto plates of various media. At least one plate should also be nutritionally complete to ensure that cells are being properly transferred between the plates. The other plates lack specific nutrients, allowing the researcher to discover various auxotrophic mutants unable to produce specific nutrients. Cells from the corresponding colony on the nutritionally complete plate can be used to recover the mutant for further study.

The Ames Test

The Ames test, developed by Bruce Ames (1928–) in the 1970s, is a method that uses bacteria for rapid, inexpensive screening of the carcinogenic potential of new chemical compounds. The test measures the mutation rate associated with exposure to the compound, which, if elevated, may indicate that exposure to this compound is associated with greater cancer risk. The Ames test uses as the test organism a strain of Salmonella typhimurium that is a histidine auxotroph, unable to synthesize its own histidine because of a mutation in an essential gene required for its synthesis. After exposure to a potential mutagen, these bacteria are plated onto a medium lacking histidine, and the number of mutants regaining the ability to synthesize histidine is recorded and compared with the number of such mutants that arise in the absence of the potential mutagen (Figure 11.25). Chemicals that are more mutagenic will bring about more mutants with restored histidine synthesis in the Ames test. Because many chemicals are not directly mutagenic but are metabolized to mutagenic forms by liver enzymes, rat liver extract is commonly included at the start of this experiment to mimic liver metabolism. After the Ames test is conducted, compounds identified as mutagenic are further tested for their potential carcinogenic properties by using other models, including animal models like mice and rats.
Identification of auxotrophic mutants, like histidine auxotrophs, is done using replica plating. After mutagenesis, colonies that grow on nutritionally complete medium but not on medium lacking histidine are identified as histidine auxotrophs.

The Ames test is used to identify mutagenic, potentially carcinogenic chemicals. A *Salmonella* histidine auxotroph is used as the test strain, exposed to a potential mutagen/carcinogen. The number of reversion mutants capable of growing in the absence of supplied histidine is counted and compared with the number of natural reversion mutants that arise in the absence of the potential mutagen.

**Check Your Understanding**

- What mutation is used as an indicator of mutation rate in the Ames test?
11.6 How Asexual Prokaryotes Achieve Genetic Diversity

Learning Objectives

• Compare the processes of transformation, transduction, and conjugation

• Explain how asexual gene transfer results in prokaryotic genetic diversity

• Explain the structure and consequences for bacterial genetic diversity of transposons

Typically, when we consider genetic transfer, we think of **vertical gene transfer**, the transmission of genetic information from generation to generation. Vertical gene transfer is by far the main mode of transmission of genetic information in all cells. In sexually reproducing organisms, crossing-over events and independent assortment of individual chromosomes during meiosis contribute to genetic diversity in the population. Genetic diversity is also introduced during sexual reproduction, when the genetic information from two parents, each with different complements of genetic information, are combined, producing new combinations of parental genotypes in the diploid offspring. The occurrence of mutations also contributes to genetic diversity in a population. Genetic diversity of offspring is useful in changing or inconsistent environments and may be one reason for the evolutionary success of sexual reproduction.

When prokaryotes and eukaryotes reproduce asexually, they transfer a nearly identical copy of their genetic material to their offspring through vertical gene transfer. Although asexual reproduction produces more offspring more quickly, any benefits of diversity among those offspring are lost. How then do organisms whose dominant reproductive mode is asexual create genetic diversity? In prokaryotes, **horizontal gene transfer (HGT)**, the introduction of genetic material from one organism to another organism within the same generation, is an important way to introduce genetic diversity. HGT allows even distantly related species to share genes, influencing their phenotypes. It is thought that HGT is more prevalent in prokaryotes but that only a small fraction of the prokaryotic genome may be transferred by this type of transfer at any one time. As the phenomenon is investigated more thoroughly, it may be revealed to be even more common. Many scientists believe that HGT and mutation are significant sources of genetic variation, the raw material for the process of natural selection, in prokaryotes. Although HGT is more common among evolutionarily related organisms, it may occur between any two species that live together in a natural community.

HGT in prokaryotes is known to occur by the three primary mechanisms that are illustrated in Figure 11.26:

1. Transformation: naked DNA is taken up from the environment
2. Transduction: genes are transferred between cells in a virus (see The Viral Life Cycle)
3. Conjugation: use of a hollow tube called a conjugation pilus to transfer genes between cells
There are three prokaryote-specific mechanisms leading to horizontal gene transfer in prokaryotes. a) In transformation, the cell takes up DNA directly from the environment. The DNA may remain separate as a plasmid or be incorporated into the host genome. b) In transduction, a bacteriophage injects DNA that is a hybrid of viral DNA and DNA from a previously infected bacterial cell. c) In conjugation, DNA is transferred between cells through a cytoplasmic bridge after a conjugation pilus draws the two cells close enough to form the bridge.

**Check Your Understanding**

- What are three ways sexual reproduction introduces genetic variation into offspring?
- What is a benefit of asexual reproduction?
- What are the three mechanisms of horizontal gene transfer in prokaryotes?

**Transformation**

Frederick Griffith was the first to demonstrate the process of transformation. In 1928, he showed that live, nonpathogenic *Streptococcus pneumoniae* bacteria could be transformed into pathogenic bacteria through exposure to a heat-killed pathogenic strain. He concluded that some sort of agent, which he called the “transforming principle,” had been passed from the dead pathogenic bacteria to the live, nonpathogenic bacteria. In 1944, Oswald Avery (1877–1955), Colin MacLeod (1909–1972), and Maclyn McCarty (1911–2005) demonstrated that the transforming principle was DNA (see *Using Microorganisms to Discover the Secrets of Life*).

In transformation, the prokaryote takes up naked DNA found in its environment and that is derived from other cells that have lysed on death and released their contents, including their genome, into the environment. Many bacteria are naturally competent, meaning that they actively bind to environmental DNA, transport it across their cell envelopes into their cytoplasm, and make it single stranded. Typically, double-stranded foreign DNA within cells is destroyed by nucleases as a defense against viral infection. However, these nucleases are usually ineffective against single-stranded DNA, so this single-stranded DNA within the cell has the opportunity to recombine into the bacterial genome. A molecule of DNA that contains fragments of DNA from different organisms is called recombinant DNA. (Recombinant DNA will be discussed in more detail in *Microbes and the Tools of Genetic Engineering*.) If the bacterium incorporates the new DNA into its own genome through recombination, the bacterial cell may gain new phenotypic properties. For example, if a nonpathogenic bacterium takes up DNA for a toxin gene from a pathogen and then incorporates it into its chromosome, it, too, may become pathogenic. Plasmid DNA may also be taken up by competent bacteria and confer new properties to the cell. Overall, transformation in nature is a relatively inefficient process because environmental DNA levels are low because of the activity of nucleases that are also
released during cellular lysis. Additionally, genetic recombination is inefficient at incorporating new DNA sequences into the genome.

In nature, bacterial transformation is an important mechanism for the acquisition of genetic elements encoding virulence factors and antibiotic resistance. Genes encoding resistance to antimicrobial compounds have been shown to be widespread in nature, even in environments not influenced by humans. These genes, which allow microbes living in mixed communities to compete for limited resources, can be transferred within a population by transformation, as well as by the other processes of HGT. In the laboratory, we can exploit the natural process of bacterial transformation for genetic engineering to make a wide variety of medicinal products, as discussed in *Microbes and the Tools of Genetic Engineering*.

**Transduction**

Viruses that infect bacteria (bacteriophages) may also move short pieces of chromosomal DNA from one bacterium to another in a process called transduction (see Figure 6.9). Recall that in generalized transduction, any piece of chromosomal DNA may be transferred to a new host cell by accidental packaging of chromosomal DNA into a phage head during phage assembly. By contrast, specialized transduction results from the imprecise excision of a lysogenic prophage from the bacterial chromosome such that it carries with it a piece of the bacterial chromosome from either side of the phage’s integration site to a new host cell. As a result, the host may acquire new properties. This process is called lysogenic conversion. Of medical significance, a lysogenic phage may carry with it a virulence gene to its new host. Once inserted into the new host’s chromosome, the new host may gain pathogenicity. Several pathogenic bacteria, including *Corynebacterium diphtheriae* (the causative agent of diphtheria) and *Clostridium botulinum* (the causative agent of botulism), are virulent because of the introduction of toxin-encoding genes by lysogenic bacteriophages, affirming the clinical relevance of transduction in the exchange of genes involved in infectious disease. Archaea have their own viruses that translocate genetic material from one individual to another.

**Check Your Understanding**

- Why does a bacterial cell make environmental DNA brought into the cell into a single-stranded form?

---

**Case in Point**

The Clinical Consequences of Transduction

Paul, a 23-year-old relief worker from Atlanta, traveled to Haiti in 2011 to provide aid following the 2010 earthquake. After working there for several weeks, he suddenly began experiencing abdominal distress, including severe cramping, nausea, vomiting, and watery diarrhea. He also began to experience intense muscle cramping. At a local clinic, the physician suspected that Paul's symptoms were caused by cholera because there had been a cholera outbreak after the earthquake. Because cholera is transmitted by the fecal-oral route, breaches in sanitation infrastructure, such as often occur following natural disasters, may precipitate outbreaks. The physician confirmed the presumptive diagnosis using a cholera dipstick test. He
then prescribed Paul a single dose of doxycycline, as well as oral rehydration salts, instructing him to drink significant amounts of clean water.

Cholera is caused by the gram-negative curved rod *Vibrio cholerae* (Figure 11.27). Its symptoms largely result from the production of the cholera toxin (CT), which ultimately activates a chloride transporter to pump chloride ions out of the epithelial cells into the gut lumen. Water then follows the chloride ions, causing the prolific watery diarrhea characteristic of cholera. The gene encoding the cholera toxin is incorporated into the bacterial chromosome of *V. cholerae* through infection of the bacterium with the lysogenic filamentous CTX phage, which carries the CT gene and introduces it into the chromosome on integration of the prophage. Thus, pathogenic strains of *V. cholerae* result from horizontal gene transfer by specialized transduction.

- Why are outbreaks of cholera more common as a result of a natural disaster?
- Why is muscle cramping a common symptom of cholera? Why is treatment with oral rehydration salts so important for the treatment of cholera?
- In areas stricken by cholera, what are some strategies that people could use to prevent disease transmission?

![Figure 11.27](image)

**Figure 11.27** A scanning electron micrograph of *Vibrio cholerae* shows its characteristic curved rod shape.

### Conjugation

In **conjugation**, DNA is directly transferred from one prokaryote to another by means of a **conjugation pilus**, which brings the organisms into contact with one another. In *E. coli*, the genes encoding the ability to conjugate are located on a bacterial plasmid called the **F plasmid**, also known as the **fertility factor**, and the conjugation pilus is called the **F pilus**. The F-plasmid genes encode both the proteins composing the F pilus and those involved in rolling circle replication of the plasmid. Cells containing the F plasmid, capable of forming an F pilus, are called **F<sup>+</sup> cells** or **donor cells**, and those lacking an F plasmid are called **F<sup>−</sup> cells** or **recipient cells**.

#### Conjugation of the F Plasmid

During typical conjugation in *E. coli*, the F pilus of an F<sup>+</sup> cell comes into contact with an F<sup>−</sup> cell and retracts, bringing the two cell envelopes into contact (Figure 11.28). Then a cytoplasmic bridge forms between the two cells at the site of the conjugation pilus. As rolling circle replication of the F plasmid occurs in the F<sup>+</sup> cell, a single-stranded copy of the F plasmid is transferred through the cytoplasmic bridge to the F<sup>−</sup> cell, which then synthesizes the complementary strand, making it double stranded. The F<sup>−</sup> cell now becomes an F<sup>+</sup> cell capable of making its own conjugation pilus. Eventually, in a mixed bacterial population containing both F<sup>+</sup> and F<sup>−</sup> cells, all cells will become F<sup>+</sup> cells. Genes on the *E. coli* F plasmid also encode proteins preventing conjugation between F<sup>+</sup> cells.
Typical conjugation of the F plasmid from an F\(^+\) cell to an F\(^-\) cell is brought about by the conjugation pilus bringing the two cells into contact. A single strand of the F plasmid is transferred to the F\(^-\) cell, which is then made double stranded.

Conjugation of F\(^+\) and Hfr Cells

Although typical conjugation in \textit{E. coli} results in the transfer of the F-plasmid DNA only, conjugation may also transfer chromosomal DNA. This is because the F plasmid occasionally integrates into the bacterial chromosome through recombination between the plasmid and the chromosome, forming an Hfr cell (Figure 11.29). “Hfr” refers to the high frequency of recombination seen when recipient F\(^-\) cells receive genetic information from Hfr cells through conjugation. Similar to the imprecise excision of a prophage during specialized transduction, the integrated F plasmid may also be imprecisely excised from the chromosome, producing an F\(^+\) plasmid that carries with it some chromosomal DNA adjacent to the integration site. On conjugation, this DNA is introduced to the recipient cell and may be either maintained as part of the F\(^+\) plasmid or be recombined into the recipient cell’s bacterial chromosome.

Hfr cells may also treat the bacterial chromosome like an enormous F plasmid and attempt to transfer a copy of it to a recipient F\(^-\) cell. Because the bacterial chromosome is so large, transfer of the entire chromosome takes a long time (Figure 11.30). However, contact between bacterial cells during conjugation is transient, so it is unusual for the entire chromosome to be transferred. Host chromosomal DNA near the integration site of the F plasmid, displaced by the unidirectional process of rolling circle replication, is more likely to be transferred and recombined into a recipient cell’s chromosome than host genes farther away. Thus, the relative location of bacterial genes on the Hfr cell’s genome can be mapped based on when they are transferred through conjugation. As a result, prior to the age of widespread bacterial genome sequencing, distances on prokaryotic genome maps were often measured in minutes.
Figure 11.29 (a) The F plasmid can occasionally integrate into the bacterial chromosome, producing an Hfr cell. (b) Imprecise excision of the F plasmid from the chromosome of an Hfr cell may lead to the production of an F′ plasmid that carries chromosomal DNA adjacent to the integration site. This F′ plasmid can be transferred to an F− cell by conjugation.

Figure 11.30 (a) An Hfr cell may attempt to transfer the entire bacterial chromosome to an F− cell, treating the chromosome like an extremely large F plasmid. However, contact between cells during conjugation is temporary. Chromosomal genes closest to the integration site (gene 1) that are first displaced during rolling circle replication will be transferred more quickly than genes far away from the integration site (gene 4). Hence, they are more likely to be recombined into the recipient F− cell’s chromosome. (b) The time it takes for a gene to be transferred, as detected by recombination into the F− cell’s chromosome, can be used to generate a map of the bacterial genome, such as this genomic map of E. coli. Note that it takes approximately 100 minutes for the entire genome (4.6 Mbp) of an Hfr strain of E. coli to be transferred by conjugation.

**Consequences and Applications of Conjugation**

Plasmids are an important type of extrachromosomal DNA element in bacteria and, in those cells that harbor them, are considered to be part of the bacterial genome. From a clinical perspective, plasmids often code for genes involved in virulence. For example, genes encoding proteins that make a bacterial cell resistant to a particular antibiotic are encoded on R plasmids. R plasmids, in addition to their genes for antimicrobial resistance, contain genes that control conjugation and transfer of the plasmid. R plasmids are able to transfer between cells of the same species and between cells of different species. Single R plasmids commonly contain multiple genes conferring resistance to multiple antibiotics.
Genes required for the production of various toxins and molecules important for colonization during infection may also be found encoded on plasmids. For example, verotoxin-producing strains of *E. coli* (VTEC) appear to have acquired the genes encoding the Shiga toxin from its gram-negative relative *Shigella dysenteriae* through the acquisition of a large plasmid encoding this toxin. VTEC causes severe diarrheal disease that may result in hemolytic uremic syndrome (HUS), which may be lead to kidney failure and death.

In nonclinical settings, bacterial genes that encode metabolic enzymes needed to degrade specialized atypical compounds like polycyclic aromatic hydrocarbons (PAHs) are also frequently encoded on plasmids. Additionally, certain plasmids have the ability to move from bacterial cells to other cell types, like those of plants and animals, through mechanisms distinct from conjugation. Such mechanisms and their use in genetic engineering are covered in *Modern Applications of Microbial Genetics*.

**Transposition**

Genetic elements called transposons (transposable elements), or “jumping genes,” are molecules of DNA that include special inverted repeat sequences at their ends and a gene encoding the enzyme transposase (Figure 11.31). Transposons allow the entire sequence to independently excise from one location in a DNA molecule and integrate into the DNA elsewhere through a process called transposition. Transposons were originally discovered in maize (corn) by American geneticist Barbara McClintock (1902–1992) in the 1940s. Transposons have since been found in all types of organisms, both prokaryotes and eukaryotes. Thus, unlike the three previous mechanisms discussed, transposition is not prokaryote-specific. Most transposons are nonreplicative, meaning they move in a “cut-and-paste” fashion. Some may be replicative, however, retaining their location in the DNA while making a copy to be inserted elsewhere (“copy and paste”). Because transposons can move within a DNA molecule, from one DNA molecule to another, or even from one cell to another, they have the ability to introduce genetic diversity. Movement within the same DNA molecule can alter phenotype by inactivating or activating a gene.

Transposons may carry with them additional genes, moving these genes from one location to another with them. For example, bacterial transposons can relocate antibiotic resistance genes, moving them from chromosomes to plasmids. This mechanism has been shown to be responsible for the colocalization of multiple antibiotic resistance genes on a single R plasmid in *Shigella* strains causing bacterial dysentery. Such an R plasmid can then be easily transferred among a bacterial population through the process of conjugation.

**Check Your Understanding**

- What type of replication occurs during conjugation?
- What occurs to produce an Hfr *E. coli* cell?
- What types of traits are encoded on plasmids?
Transposons are segments of DNA that have the ability to move from one location to another because they code for the enzyme transposase. In this example, a nonreplicative transposon has disrupted gene B. The consequence of that the transcription of gene B may now have been interrupted.

**Check Your Understanding**

- What are two ways a transposon can affect the phenotype of a cell it moves to?

Table 11.5 summarizes the processes discussed in this section.

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conjugation</td>
<td>Transfer of DNA through direct contact using a conjugation pilus</td>
</tr>
<tr>
<td>Transduction</td>
<td>Mechanism of horizontal gene transfer in bacteria in which genes are transferred through viral infection</td>
</tr>
<tr>
<td>Transformation</td>
<td>Mechanism of horizontal gene transfer in which naked environmental DNA is taken up by a bacterial cell</td>
</tr>
<tr>
<td>Transposition</td>
<td>Process whereby DNA independently excises from one location in a DNA molecule and integrates elsewhere</td>
</tr>
</tbody>
</table>

**Clinical Focus**

**Part 3**

Despite continued antibiotic treatment, Mark's infection continued to progress rapidly. The infected region continued to expand, and he had to be put on a ventilator to help him breathe. Mark's physician ordered surgical removal of the infected tissue. Following an initial surgery, Mark's wound was monitored daily to ensure that the infection did not return, but it continued to spread.
After two additional rounds of surgery, the infection finally seemed to be contained. A few days later, Mark was removed from the ventilator and was able to breathe on his own. However, he had lost a great deal of skin and soft tissue on his lower leg.

- Why does the removal of infected tissue stem the infection?
- What are some likely complications of this method of treatment?

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

11.7 Gene Regulation: Operon Theory

Learning Objectives

- Compare inducible operons and repressible operons
- Describe why regulation of operons is important

Each nucleated cell in a multicellular organism contains copies of the same DNA. Similarly, all cells in two pure bacterial cultures inoculated from the same starting colony contain the same DNA, with the exception of changes that arise from spontaneous mutations. If each cell in a multicellular organism has the same DNA, then how is it that cells in different parts of the organism’s body exhibit different characteristics? Similarly, how is it that the same bacterial cells within two pure cultures exposed to different environmental conditions can exhibit different phenotypes? In both cases, each genetically identical cell does not turn on, or express, the same set of genes. Only a subset of proteins in a cell at a given time is expressed.

Genomic DNA contains both structural genes, which encode products that serve as cellular structures or enzymes, and regulatory genes, which encode products that regulate gene expression. The expression of a gene is a highly regulated process. Whereas regulating gene expression in multicellular organisms allows for cellular differentiation, in single-celled organisms like prokaryotes, it primarily ensures that a cell’s resources are not wasted making proteins that the cell does not need at that time.

Elucidating the mechanisms controlling gene expression is important to the understanding of human health. Malfunctions in this process in humans lead to the development of cancer and other diseases. Understanding the interaction between the gene expression of a pathogen and that of its human host is important for the understanding of a particular infectious disease. Gene regulation involves a complex web of interactions within a given cell among signals from the cell’s environment, signaling molecules within the cell, and the cell’s DNA. These interactions lead to the expression of some genes and the suppression of others, depending on circumstances.

Prokaryotes and eukaryotes share some similarities in their mechanisms to regulate gene expression; however, gene expression in eukaryotes is more complicated because of the temporal and spatial separation between the processes of transcription and translation. Thus, although most regulation of gene expression occurs through transcriptional control in prokaryotes, regulation of gene expression in eukaryotes occurs at the transcriptional level and post-transcriptionally (after the primary transcript has been made).

Prokaryotic Gene Regulation

In bacteria and archaea, structural proteins with related functions are usually encoded together within the genome in a block called an operon and are transcribed together under the control of a single promoter, resulting in the formation of a polycistronic transcript (Figure 11.32). In this way, regulation of the transcription of all of the structural genes encoding the enzymes that catalyze the many steps in a single biochemical pathway can be controlled simultaneously, because they will either all be needed at the same time, or none will be needed. For example, in *E. coli*, all of the structural genes that encode enzymes needed to use lactose as an energy source lie next to each other in the lactose (or...
lac operon under the control of a single promoter, the lac promoter. French scientists François Jacob (1920–2013) and Jacques Monod at the Pasteur Institute were the first to show the organization of bacterial genes into operons, through their studies on the lac operon of *E. coli*. For this work, they won the Nobel Prize in Physiology or Medicine in 1965. Although eukaryotic genes are not organized into operons, prokaryotic operons are excellent models for learning about gene regulation generally. There are some gene clusters in eukaryotes that function similar to operons. Many of the principles can be applied to eukaryotic systems and contribute to our understanding of changes in gene expression in eukaryotes that can result in pathological changes such as cancer.

Each operon includes DNA sequences that influence its own transcription; these are located in a region called the regulatory region. The regulatory region includes the promoter and the region surrounding the promoter, to which transcription factors, proteins encoded by regulatory genes, can bind. Transcription factors influence the binding of RNA polymerase to the promoter and allow its progression to transcribe structural genes. A repressor is a transcription factor that suppresses transcription of a gene in response to an external stimulus by binding to a DNA sequence within the regulatory region called the operator, which is located between the RNA polymerase binding site of the promoter and the transcriptional start site of the first structural gene. Repressor binding physically blocks RNA polymerase from transcribing structural genes. Conversely, an activator is a transcription factor that increases the transcription of a gene in response to an external stimulus by facilitating RNA polymerase binding to the promoter. An inducer, a third type of regulatory molecule, is a small molecule that either activates or represses transcription by interacting with a repressor or an activator.

In prokaryotes, there are examples of operons whose gene products are required rather consistently and whose expression, therefore, is unregulated. Such operons are constitutively expressed, meaning they are transcribed and translated continuously to provide the cell with constant intermediate levels of the protein products. Such genes encode enzymes involved in housekeeping functions required for cellular maintenance, including DNA replication, repair, and expression, as well as enzymes involved in core metabolism. In contrast, there are other prokaryotic operons that are expressed only when needed and are regulated by repressors, activators, and inducers.

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Figure 11.32 In prokaryotes, structural genes of related function are often organized together on the genome and transcribed together under the control of a single promoter. The operon’s regulatory region includes both the promoter and the operator. If a repressor binds to the operator, then the structural genes will not be transcribed. Alternatively, activators may bind to the regulatory region, enhancing transcription.

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**Check Your Understanding**

- What are the parts in the DNA sequence of an operon?
What types of regulatory molecules are there?

Regulation by Repression

Prokaryotic operons are commonly controlled by the binding of repressors to operator regions, thereby preventing the transcription of the structural genes. Such operons are classified as either repressible operons or inducible operons. Repressible operons, like the tryptophan (trp) operon, typically contain genes encoding enzymes required for a biosynthetic pathway. As long as the product of the pathway, like tryptophan, continues to be required by the cell, a repressible operon will continue to be expressed. However, when the product of the biosynthetic pathway begins to accumulate in the cell, removing the need for the cell to continue to make more, the expression of the operon is repressed. Conversely, inducible operons, like the lac operon of E. coli, often contain genes encoding enzymes in a pathway involved in the metabolism of a specific substrate like lactose. These enzymes are only required when that substrate is available, thus expression of the operons is typically induced only in the presence of the substrate.

The trp Operon: A Repressible Operon

E. coli can synthesize tryptophan using enzymes that are encoded by five structural genes located next to each other in the trp operon (Figure 11.33). When environmental tryptophan is low, the operon is turned on. This means that transcription is initiated, the genes are expressed, and tryptophan is synthesized. However, if tryptophan is present in the environment, the trp operon is turned off. Transcription does not occur and tryptophan is not synthesized.

When tryptophan is not present in the cell, the repressor by itself does not bind to the operator; therefore, the operon is active and tryptophan is synthesized. However, when tryptophan accumulates in the cell, two tryptophan molecules bind to the trp repressor molecule, which changes its shape, allowing it to bind to the trp operator. This binding of the active form of the trp repressor to the operator blocks RNA polymerase from transcribing the structural genes, stopping expression of the operon. Thus, the actual product of the biosynthetic pathway controlled by the operon regulates the expression of the operon.

Figure 11.33  The five structural genes needed to synthesize tryptophan in E. coli are located next to each other in the trp operon. When tryptophan is absent, the repressor protein does not bind to the operator, and the genes are transcribed. When tryptophan is plentiful, tryptophan binds the repressor protein at the operator sequence. This physically blocks the RNA polymerase from transcribing the tryptophan biosynthesis genes.
The lac Operon: An Inducible Operon

The lac operon is an example of an inducible operon that is also subject to activation in the absence of glucose (Figure 11.34). The lac operon encodes three structural genes necessary to acquire and process the disaccharide lactose from the environment, breaking it down into the simple sugars glucose and galactose. For the lac operon to be expressed, lactose must be present. This makes sense for the cell because it would be energetically wasteful to create the enzymes to process lactose if lactose was not available.

In the absence of lactose, the lac repressor is bound to the operator region of the lac operon, physically preventing RNA polymerase from transcribing the structural genes. However, when lactose is present, the lactose inside the cell is converted to allolactose. Allolactose serves as an inducer molecule, binding to the repressor and changing its shape so that it is no longer able to bind to the operator DNA. Removal of the repressor in the presence of lactose allows RNA polymerase to move through the operator region and begin transcription of the lac structural genes.

Figure 11.34 The three structural genes that are needed to degrade lactose in E. coli are located next to each other in the lac operon. When lactose is absent, the repressor protein binds to the operator, physically blocking the RNA polymerase from transcribing the lac structural genes. When lactose is available, a lactose molecule binds the repressor protein, preventing the repressor from binding to the operator sequence, and the genes are transcribed.

The lac Operon: Activation by Catabolite Activator Protein

Bacteria typically have the ability to use a variety of substrates as carbon sources. However, because glucose is usually preferable to other substrates, bacteria have mechanisms to ensure that alternative substrates are only used when glucose has been depleted. Additionally, bacteria have mechanisms to ensure that the genes encoding enzymes for using alternative substrates are expressed only when the alternative substrate is available. In the 1940s, Jacques Monod was the first to demonstrate the preference for certain substrates over others through his studies of E. coli’s growth when cultured in the presence of two different substrates simultaneously. Such studies generated diauxic growth curves, like the one shown in Figure 11.35. Although the preferred substrate glucose is used first, E. coli
grows quickly and the enzymes for lactose metabolism are absent. However, once glucose levels are depleted, growth rates slow, inducing the expression of the enzymes needed for the metabolism of the second substrate, lactose. Notice how the growth rate in lactose is slower, as indicated by the lower steepness of the growth curve.

The ability to switch from glucose use to another substrate like lactose is a consequence of the activity of an enzyme called Enzyme IIA (EIIA). When glucose levels drop, cells produce less ATP from catabolism (see Catabolism of Carbohydrates), and EIIA becomes phosphorylated. Phosphorylated EIIA activates adenyl cyclase, an enzyme that converts some of the remaining ATP to cyclic AMP (cAMP), a cyclic derivative of AMP and important signaling molecule involved in glucose and energy metabolism in E. coli. As a result, cAMP levels begin to rise in the cell (Figure 11.36).

The lac operon also plays a role in this switch from using glucose to using lactose. When glucose is scarce, the accumulating cAMP caused by increased adenyl cyclase activity binds to catabolite activator protein (CAP), also known as cAMP receptor protein (CRP). The complex binds to the promoter region of the lac operon (Figure 11.37). In the regulatory regions of these operons, a CAP binding site is located upstream of the RNA polymerase binding site in the promoter. Binding of the CAP-cAMP complex to this site increases the binding ability of RNA polymerase to the promoter region to initiate the transcription of the structural genes. Thus, in the case of the lac operon, for transcription to occur, lactose must be present (removing the lac repressor protein) and glucose levels must be depleted (allowing binding of an activating protein). When glucose levels are high, there is catabolite repression of operons encoding enzymes for the metabolism of alternative substrates. Because of low cAMP levels under these conditions, there is an insufficient amount of the CAP-cAMP complex to activate transcription of these operons. See Table 11.6 for a summary of the regulation of the lac operon.

**Figure 11.35**  When grown in the presence of two substrates, E. coli uses the preferred substrate (in this case glucose) until it is depleted. Then, enzymes needed for the metabolism of the second substrate are expressed and growth resumes, although at a slower rate.
Figure 11.36  When ATP levels decrease due to depletion of glucose, some remaining ATP is converted to cAMP by adenylyl cyclase. Thus, increased cAMP levels signal glucose depletion.

Figure 11.37  (a) In the presence of cAMP, CAP binds to the promoters of operons, like the lac operon, that encode genes for enzymes for the use of alternate substrates. (b) For the lac operon to be expressed, there must be activation by cAMP-CAP as well as removal of the lac repressor from the operator.

<table>
<thead>
<tr>
<th>Conditions Affecting Transcription of the lac Operon</th>
</tr>
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<tbody>
<tr>
<td>Glucose</td>
</tr>
<tr>
<td>+</td>
</tr>
<tr>
<td>+</td>
</tr>
<tr>
<td>–</td>
</tr>
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<td>–</td>
</tr>
</tbody>
</table>

Table 11.6
Watch an animated tutorial (https://openstax.org/l/22lacoperon) about the workings of lac operon here.

Check Your Understanding

• What affects the binding of the trp operon repressor to the operator?
• How and when is the behavior of the lac repressor protein altered?
• In addition to being repressible, how else is the lac operon regulated?

Global Responses of Prokaryotes

In prokaryotes, there are also several higher levels of gene regulation that have the ability to control the transcription of many related operons simultaneously in response to an environmental signal. A group of operons all controlled simultaneously is called a regulon.

Alarmones

When sensing impending stress, prokaryotes alter the expression of a wide variety of operons to respond in coordination. They do this through the production of alarmones, which are small intracellular nucleotide derivatives. Alarmones change which genes are expressed and stimulate the expression of specific stress-response genes. The use of alarmones to alter gene expression in response to stress appears to be important in pathogenic bacteria. On encountering host defense mechanisms and other harsh conditions during infection, many operons encoding virulence genes are upregulated in response to alarmone signaling. Knowledge of these responses is key to being able to fully understand the infection process of many pathogens and to the development of therapies to counter this process.

Alternate σ Factors

Since the σ subunit of bacterial RNA polymerase confers specificity as to which promoters should be transcribed, altering the σ factor used is another way for bacteria to quickly and globally change what regulons are transcribed at a given time. The σ factor recognizes sequences within a bacterial promoter, so different σ factors will each recognize slightly different promoter sequences. In this way, when the cell senses specific environmental conditions, it may respond by changing which σ factor it expresses, degrading the old one and producing a new one to transcribe the operons encoding genes whose products will be useful under the new environmental condition. For example, in sporulating bacteria of the genera Bacillus and Clostridium (which include many pathogens), a group of σ factors controls the expression of the many genes needed for sporulation in response to sporulation-stimulating signals.

Check Your Understanding

• What is the name given to a collection of operons that can be regulated as a group?
• What type of stimulus would trigger the transcription of a different σ factor?
Additional Methods of Regulation in Bacteria: Attenuation and Riboswitches

Although most gene expression is regulated at the level of transcription initiation in prokaryotes, there are also mechanisms to control both the completion of transcription as well as translation concurrently. Since their discovery, these mechanisms have been shown to control the completion of transcription and translation of many prokaryotic operons. Because these mechanisms link the regulation of transcription and translation directly, they are specific to prokaryotes, because these processes are physically separated in eukaryotes.

One such regulatory system is **attenuation**, whereby secondary stem-loop structures formed within the 5’ end of an mRNA being transcribed determine if transcription to complete the synthesis of this mRNA will occur and if this mRNA will be used for translation. Beyond the transcriptional repression mechanism already discussed, attenuation also controls expression of the *trp* operon in *E. coli* (Figure 11.38). The *trp* operon regulatory region contains a leader sequence called *trpL* between the operator and the first structural gene, which has four stretches of RNA that can base pair with each other in different combinations. When a terminator stem-loop forms, transcription terminates, releasing RNA polymerase from the mRNA. However, when an antiterminator stem-loop forms, this prevents the formation of the terminator stem-loop, so RNA polymerase can transcribe the structural genes.

A related mechanism of concurrent regulation of transcription and translation in prokaryotes is the use of a **riboswitch**, a small region of noncoding RNA found within the 5’ end of some prokaryotic mRNA molecules (Figure 11.39. A riboswitch may bind to a small intracellular molecule to stabilize certain secondary structures of the mRNA molecule. The binding of the small molecule determines which stem-loop structure forms, thus influencing the completion of mRNA synthesis and protein synthesis.
Figure 11.38  When tryptophan is plentiful, translation of the short leader peptide encoded by trpL proceeds, the terminator loop between regions 3 and 4 forms, and transcription terminates. When tryptophan levels are depleted, translation of the short leader peptide stalls at region 1, allowing regions 2 and 3 to form an antiterminator loop, and RNA polymerase can transcribe the structural genes of the trp operon.
Riboswitches found within prokaryotic mRNA molecules can bind to small intracellular molecules, stabilizing certain RNA structures, influencing either the completion of the synthesis of the mRNA molecule itself (left) or the protein made using that mRNA (right).

Other Factors Affecting Gene Expression in Prokaryotes and Eukaryotes

Although the focus on our discussion of transcriptional control used prokaryotic operons as examples, eukaryotic transcriptional control is similar in many ways. As in prokaryotes, eukaryotic transcription can be controlled through the binding of transcription factors including repressors and activators. Interestingly, eukaryotic transcription can be influenced by the binding of proteins to regions of DNA, called enhancers, rather far away from the gene, through DNA looping facilitated between the enhancer and the promoter (Figure 11.40). Overall, regulating transcription is a highly effective way to control gene expression in both prokaryotes and eukaryotes. However, the control of gene expression in eukaryotes in response to environmental and cellular stresses can be accomplished in additional ways without the binding of transcription factors to regulatory regions.
In eukaryotes, an enhancer is a DNA sequence that promotes transcription. Each enhancer is made up of short DNA sequences called distal control elements. Activators bound to the distal control elements interact with mediator proteins and transcription factors. Two different genes may have the same promoter but different distal control elements, enabling differential gene expression.

**DNA-Level Control**

In eukaryotes, the DNA molecules or associated histones can be chemically modified in such a way as to influence transcription; this is called **epigenetic regulation**. Methylation of certain cytosine nucleotides in DNA in response to environmental factors has been shown to influence use of such DNA for transcription, with DNA methylation commonly correlating to lowered levels of gene expression. Additionally, in response to environmental factors, histone proteins for packaging DNA can also be chemically modified in multiple ways, including acetylation and deacetylation, influencing the packaging state of DNA and thus affecting the availability of loosely wound DNA for transcription. These chemical modifications can sometimes be maintained through multiple rounds of cell division, making at least some of these epigenetic changes heritable.

**Link to Learning**

This video (https://openstax.org/l/22epigreg) describes how epigenetic regulation controls gene expression.

**Check Your Understanding**

- What stops or allows transcription to proceed when attenuation is operating?
- What determines the state of a riboswitch?
- Describe the function of an enhancer.
- Describe two mechanisms of epigenetic regulation in eukaryotes.
Although Mark survived his bout with necrotizing fasciitis, he would now have to undergo a skin-grafting surgery, followed by long-term physical therapy. Based on the amount of muscle mass he lost, it is unlikely that his leg will return to full strength, but his physical therapist is optimistic that he will regain some use of his leg.

Laboratory testing revealed the causative agent of Mark’s infection was a strain of group A streptococcus (Group A strep). As required by law, Mark’s case was reported to the state health department and ultimately to the Centers for Disease Control and Prevention (CDC). At the CDC, the strain of group A strep isolated from Mark was analyzed more thoroughly for methicillin resistance.

Methicillin resistance is genetically encoded and is becoming more common in group A strep through horizontal gene transfer. In necrotizing fasciitis, blood flow to the infected area is typically limited because of the action of various genetically encoded bacterial toxins. This is why there is typically little to no bleeding as a result of the incision test. Unfortunately, these bacterial toxins limit the effectiveness of intravenous antibiotics in clearing infection from the skin and underlying tissue, meaning that antibiotic resistance alone does not explain the ineffectiveness of Mark’s treatment. Nevertheless, intravenous antibiotic therapy was warranted to help minimize the possible outcome of sepsis, which is a common outcome of necrotizing fasciitis. Through genomic analysis by the CDC of the strain isolated from Mark, several of the important virulence genes were shown to be encoded on prophages, indicating that transduction is important in the horizontal gene transfer of these genes from one bacterial cell to another.

Go back to the previous Clinical Focus box.

Summary

11.1 The Functions of Genetic Material
- DNA serves two important cellular functions: It is the genetic material passed from parent to offspring and it serves as the information to direct and regulate the construction of the proteins necessary for the cell to perform all of its functions.

- The central dogma states that DNA organized into genes specifies the sequences of messenger RNA (mRNA), which, in turn, specifies the amino acid sequence of proteins.

- The genotype of a cell is the full collection of genes a cell contains. Not all genes are used to make proteins simultaneously. The phenotype is a cell’s observable characteristics resulting from the proteins it is producing at a given time under specific environmental conditions.

11.2 DNA Replication
- The DNA replication process is semiconservative, which results in two DNA molecules, each having one parental strand of DNA and one newly synthesized strand.

- In bacteria, the initiation of replication occurs at the origin of replication, where supercoiled DNA is unwound by DNA gyrase, made single-stranded by helicase, and bound by single-stranded binding protein to maintain its single-stranded state. Primase synthesizes a short RNA primer, providing a free 3’-OH group to which DNA polymerase III can add DNA nucleotides.

- During elongation, the leading strand of DNA is synthesized continuously from a single primer. The lagging strand is synthesized discontinuously in short Okazaki fragments, each requiring its own primer. The RNA primers are removed and replaced with DNA nucleotides by bacterial DNA polymerase I, and DNA ligase seals the gaps between these fragments.

- Termination of replication in bacteria involves the resolution of circular DNA concatemers by topoisomerase IV to release the two copies of the circular chromosome.
• Eukaryotes typically have multiple linear chromosomes, each with multiple origins of replication. Overall, replication in eukaryotes is similar to that in prokaryotes.
• The linear nature of eukaryotic chromosomes necessitates telomeres to protect genes near the end of the chromosomes. Telomerase extends telomeres, preventing their degradation, in some cell types.
• Rolling circle replication is a type of rapid unidirectional DNA synthesis of a circular DNA molecule used for the replication of some plasmids.

11.3 RNA Transcription
• During transcription, the information encoded in DNA is used to make RNA.
• RNA polymerase synthesizes RNA, using the antisense strand of the DNA as template by adding complementary RNA nucleotides to the 3’ end of the growing strand.
• RNA polymerase binds to DNA at a sequence called a promoter during the initiation of transcription.
• Genes encoding proteins of related functions are frequently transcribed under the control of a single promoter in prokaryotes, resulting in the formation of a polycistronic mRNA molecule that encodes multiple polypeptides.
• Unlike DNA polymerase, RNA polymerase does not require a 3’-OH group to add nucleotides, so a primer is not needed during initiation.
• Termination of transcription in bacteria occurs when the RNA polymerase encounters specific DNA sequences that lead to stalling of the polymerase. This results in release of RNA polymerase from the DNA template strand, freeing the RNA transcript.
• Eukaryotes have three different RNA polymerases. Eukaryotes also have monocistronic mRNA, each encoding only a single polypeptide.
• Eukaryotic primary transcripts are processed in several ways, including the addition of a 5’ cap and a 3′-poly-A tail, as well as splicing, to generate a mature mRNA molecule that can be transported out of the nucleus and that is protected from degradation.

11.4 Protein Synthesis (Translation)
• In translation, polypeptides are synthesized using mRNA sequences and cellular machinery, including tRNAs that match mRNA codons to specific amino acids and ribosomes composed of RNA and proteins that catalyze the reaction.
• The genetic code is degenerate in that several mRNA codons code for the same amino acids. The genetic code is almost universal among living organisms.
• Prokaryotic (70S) and cytoplasmic eukaryotic (80S) ribosomes are each composed of a large subunit and a small subunit of differing sizes between the two groups. Each subunit is composed of rRNA and protein. Organelle ribosomes in eukaryotic cells resemble prokaryotic ribosomes.
• Some 60 to 90 species of tRNA exist in bacteria. Each tRNA has a three-nucleotide anticodon as well as a binding site for a cognate amino acid. All tRNAs with a specific anticodon will carry the same amino acid.
• Initiation of translation occurs when the small ribosomal subunit binds with initiation factors and an initiator tRNA at the start codon of an mRNA, followed by the binding to the initiation complex of the large ribosomal subunit.
• In prokaryotic cells, the start codon codes for N-formyl-methionine carried by a special initiator tRNA. In eukaryotic cells, the start codon codes for methionine carried by a special initiator tRNA. In addition, whereas ribosomal binding of the mRNA in prokaryotes is facilitated by the Shine-Dalgarno sequence within the mRNA, eukaryotic ribosomes bind to the 5’ cap of the mRNA.
• During the elongation stage of translation, a charged tRNA binds to mRNA in the A site of the ribosome; a peptide bond is catalyzed between the two adjacent amino acids, breaking the bond between the first amino acid and its tRNA; the ribosome moves one codon along the mRNA; and the first tRNA is moved from the P site of the ribosome to the E site and leaves the ribosomal complex.
Termination of translation occurs when the ribosome encounters a **stop codon**, which does not code for a tRNA. Release factors cause the polypeptide to be released, and the ribosomal complex dissociates.

In prokaryotes, transcription and translation may be coupled, with translation of an mRNA molecule beginning as soon as transcription allows enough mRNA exposure for the binding of a ribosome, prior to transcription termination. Transcription and translation are not coupled in eukaryotes because transcription occurs in the nucleus, whereas translation occurs in the cytoplasm or in association with the rough endoplasmic reticulum.

Polypeptides often require one or more **post-translational modifications** to become biologically active.

### 11.5 Mutations

- **Mutation** is a heritable change in DNA. A mutation may lead to a change in the amino-acid sequence of a protein, possibly affecting its function.

- A **point mutation** affects a single base pair. A point mutation may cause a **silent mutation** if the mRNA codon codes for the same amino acid, a **missense mutation** if the mRNA codon codes for a different amino acid, or a **nonsense mutation** if the mRNA codon becomes a stop codon.

- Missense mutations may retain function, depending on the chemistry of the new amino acid and its location in the protein. Nonsense mutations produce truncated and frequently nonfunctional proteins.

- A **frameshift mutation** results from an insertion or deletion of a number of nucleotides that is not a multiple of three. The change in reading frame alters every amino acid after the point of the mutation and results in a nonfunctional protein.

- **Spontaneous mutations** occur through DNA replication errors, whereas **induced mutations** occur through exposure to a **mutagen**.

- Mutagenic agents are frequently carcinogenic but not always. However, nearly all carcinogens are mutagenic.

- Chemical mutagens include base analogs and chemicals that modify existing bases. In both cases, mutations are introduced after several rounds of DNA replication.

- **Ionizing radiation**, such as X-rays and γ-rays, leads to breakage of the phosphodiester backbone of DNA and can also chemically modify bases to alter their base-pairing rules.

- **Nonionizing radiation** like ultraviolet light may introduce pyrimidine (thymine) dimers, which, during DNA replication and transcription, may introduce frameshift or point mutations.

- Cells have mechanisms to repair naturally occurring mutations. DNA polymerase has proofreading activity. Mismatch repair is a process to repair incorrectly incorporated bases after DNA replication has been completed.

- Pyrimidine dimers can also be repaired. In **nucleotide excision repair (dark repair)**, enzymes recognize the distortion introduced by the pyrimidine dimer and replace the damaged strand with the correct bases, using the undamaged DNA strand as a template. Bacteria and other organisms may also use **direct repair**, in which the photolyase enzyme, in the presence of visible light, breaks apart the pyrimidines.

- Through comparison of growth on the complete plate and lack of growth on media lacking specific nutrients, specific loss-of-function mutants called **auxotrophs** can be identified.

- The **Ames test** is an inexpensive method that uses auxotrophic bacteria to measure mutagenicity of a chemical compound. Mutagenicity is an indicator of carcinogenic potential.

### 11.6 How Asexual Prokaryotes Achieve Genetic Diversity

- **Horizontal gene transfer** is an important way for asexually reproducing organisms like prokaryotes to acquire new traits.

- There are three mechanisms of horizontal gene transfer typically used by bacteria: **transformation**, **transduction**, and **conjugation**.

- Transformation allows for competent cells to take up naked DNA, released from other cells on their death, into their cytoplasm, where it may recombine with the host genome.
• In **generalized transduction**, any piece of chromosomal DNA may be transferred by accidental packaging of the degraded host chromosome into a phage head. In **specialized transduction**, only chromosomal DNA adjacent to the integration site of a lysogenic phage may be transferred as a result of imprecise excision of the prophage.

• Conjugation is mediated by the **F plasmid**, which encodes a **conjugation pilus** that brings an F plasmid-containing F' cell into contact with an F' cell.

• The rare integration of the F plasmid into the bacterial chromosome, generating an Hfr cell, allows for transfer of chromosomal DNA from the donor to the recipient. Additionally, imprecise excision of the F plasmid from the chromosome may generate an F' plasmid that may be transferred to a recipient by conjugation.

• Conjugation transfer of **R plasmids** is an important mechanism for the spread of antibiotic resistance in bacterial communities.

• **Transposons** are molecules of DNA with inverted repeats at their ends that also encode the enzyme transposase, allowing for their movement from one location in DNA to another. Although found in both prokaryotes and eukaryotes, transposons are clinically relevant in bacterial pathogens for the movement of virulence factors, including antibiotic resistance genes.

### 11.7 Gene Regulation: Operon Theory

• **Gene expression** is a tightly regulated process.

• Gene expression in prokaryotes is largely regulated at the point of transcription. Gene expression in eukaryotes is additionally regulated post-transcriptionally.

• Prokaryotic structural genes of related function are often organized into **operons**, all controlled by transcription from a single promoter. The regulatory region of an operon includes the promoter itself and the region surrounding the promoter to which transcription factors can bind to influence transcription.

• Although some operons are **constitutively expressed**, most are subject to regulation through the use of **transcription factors** (repressors and activators). A **repressor** binds to an **operator**, a DNA sequence within the regulatory region between the RNA polymerase binding site in the promoter and first structural gene, thereby physically blocking transcription of these operons. An **activator** binds within the regulatory region of an operon, helping RNA polymerase bind to the promoter, thereby enhancing the transcription of this operon. An **inducer** influences transcription through interacting with a repressor or activator.

• The **trp** operon is a classic example of a **repressible operon**. When tryptophan accumulates, tryptophan binds to a repressor, which then binds to the operator, preventing further transcription.

• The **lac** operon is a classic example an **inducible operon**. When lactose is present in the cell, it is converted to allolactose. Allolactose acts as an inducer, binding to the repressor and preventing the repressor from binding to the operator. This allows transcription of the structural genes.

• The **lac** operon is also subject to activation. When glucose levels are depleted, some cellular ATP is converted into cAMP, which binds to the **catabolite activator protein (CAP)**. The cAMP-CAP complex activates transcription of the **lac** operon. When glucose levels are high, its presence prevents transcription of the **lac** operon and other operons by **catabolite repression**.

• Small intracellular molecules called **alarmones** are made in response to various environmental stresses, allowing bacteria to control the transcription of a group of operons, called a regulon.

• Bacteria have the ability to change which **σ factor** of RNA polymerase they use in response to environmental conditions to quickly and globally change which regulons are transcribed.

• Prokaryotes have regulatory mechanisms, including **attenuation** and the use of **riboswitches**, to simultaneously control the completion of transcription and translation from that transcript. These mechanisms work through the formation of stem loops in the 5' end of an mRNA molecule currently being synthesized.

• There are additional points of regulation of gene expression in prokaryotes and eukaryotes. In eukaryotes, **epigenetic regulation** by chemical modification of DNA or histones, and regulation of RNA processing are two methods.

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**Review Questions**
Multiple Choice

1. DNA does all but which of the following?
   a. serves as the genetic material passed from parent to offspring
   b. remains constant despite changes in environmental conditions
   c. provides the instructions for the synthesis of messenger RNA
   d. is read by ribosomes during the process of translation

2. According to the central dogma, which of the following represents the flow of genetic information in cells?
   a. protein to DNA to RNA
   b. DNA to RNA to protein
   c. RNA to DNA to protein
   d. DNA to protein to RNA

3. Which of the following is the enzyme that replaces the RNA nucleotides in a primer with DNA nucleotides?
   a. DNA polymerase III
   b. DNA polymerase I
   c. primase
   d. helicase

4. Which of the following is not involved in the initiation of replication?
   a. ligase
   b. DNA gyrase
   c. single-stranded binding protein
   d. primase

5. Which of the following enzymes involved in DNA replication is unique to eukaryotes?
   a. helicase
   b. DNA polymerase
   c. ligase
   d. telomerase

6. Which of the following would be synthesized using 5'-CAGTTCGGA-3' as a template?
   a. 3'-AGGCTTGAC-4'
   b. 3'-TCCGAACGTG-5'
   c. 3'-GTCAAGCTC-5'
   d. 3'-CAGTTCGGA-5'

7. During which stage of bacterial transcription is the α subunit of the RNA polymerase involved?
   a. initiation
   b. elongation
   c. termination
   d. splicing

8. Which of the following components is involved in the initiation of transcription?
   a. primer
   b. origin
   c. promoter
   d. start codon

9. Which of the following is not a function of the 5’ cap and 3’ poly-A tail of a mature eukaryotic mRNA molecule?
   a. to facilitate splicing
   b. to prevent mRNA degradation
   c. to aid export of the mature transcript to the cytoplasm
   d. to aid ribosome binding to the transcript

10. Mature mRNA from a eukaryote would contain each of these features except which of the following?
    a. exon-encoded RNA
    b. intron-encoded RNA
    c. 5’ cap
    d. 3’ poly-A tail

11. Which of the following is the name of the three-base sequence in the mRNA that binds to a tRNA molecule?
    a. P site
    b. codon
    c. anticodon
    d. CCA binding site

12. Which component is the last to join the initiation complex during the initiation of translation?
    a. the mRNA molecule
    b. the small ribosomal subunit
    c. the large ribosomal subunit
    d. the initiator tRNA

13. During elongation in translation, to which ribosomal site does an incoming charged tRNA molecule bind?
    a. A site
    b. P site
    c. E site
    d. B site

14. Which of the following is the amino acid that appears at the N-terminus of all newly translated prokaryotic and eukaryotic polypeptides?
    a. tryptophan
    b. methionine
    c. selenocysteine
    d. glycine
15. When the ribosome reaches a nonsense codon, which of the following occurs?
   a. a methionine is incorporated
   b. the polypeptide is released
   c. a peptide bond forms
   d. the A site binds to a charged tRNA

16. Which of the following is a change in the sequence that leads to formation of a stop codon?
   a. missense mutation
   b. nonsense mutation
   c. silent mutation
   d. deletion mutation

17. The formation of pyrimidine dimers results from which of the following?
   a. spontaneous errors by DNA polymerase
   b. exposure to gamma radiation
   c. exposure to ultraviolet radiation
   d. exposure to intercalating agents

18. Which of the following is an example of a frameshift mutation?
   a. a deletion of a codon
   b. missense mutation
   c. silent mutation
   d. deletion of one nucleotide

19. Which of the following is the type of DNA repair in which thymine dimers are directly broken down by the enzyme photolyase?
   a. direct repair
   b. nucleotide excision repair
   c. mismatch repair
   d. proofreading

20. Which of the following regarding the Ames test is true?
   a. It is used to identify newly formed auxotrophic mutants.
   b. It is used to identify mutants with restored biosynthetic activity.
   c. It is used to identify spontaneous mutants.
   d. It is used to identify mutants lacking photoreactivation activity.

21. Which is the mechanism by which improper excision of a prophage from a bacterial chromosome results in packaging of bacterial genes near the integration site into a phage head?
   a. conjugation
   b. generalized transduction
   c. specialized transduction
   d. transformation

22. Which of the following refers to the uptake of naked DNA from the surrounding environment?
   a. conjugation
   b. generalized transduction
   c. specialized transduction
   d. transformation

23. The F plasmid is involved in which of the following processes?
   a. conjugation
   b. transduction
   c. transposition
   d. transformation

24. Which of the following refers to the mechanism of horizontal gene transfer naturally responsible for the spread of antibiotic resistance genes within a bacterial population?
   a. conjugation
   b. generalized transduction
   c. specialized transduction
   d. transformation

25. An operon of genes encoding enzymes in a biosynthetic pathway is likely to be which of the following?
   a. inducible
   b. repressible
   c. constitutive
   d. monocistronic

26. An operon encoding genes that are transcribed and translated continuously to provide the cell with constant intermediate levels of the protein products is said to be which of the following?
   a. repressible
   b. inducible
   c. constitutive
   d. activated

27. Which of the following conditions leads to maximal expression of the lac operon?
   a. lactose present, glucose absent
   b. lactose present, glucose present
   c. lactose absent, glucose absent
   d. lactose absent, glucose present

28. Which of the following is a type of regulation of gene expression unique to eukaryotes?
   a. attenuation
   b. use of alternate σ factor
   c. chemical modification of histones
   d. alarmones
**True/False**
29. Cells are always producing proteins from every gene they possess.
30. More primers are used in lagging strand synthesis than in leading strand synthesis.
31. Each codon within the genetic code encodes a different amino acid.
32. Carcinogens are typically mutagenic.
33. Asexually reproducing organisms lack mechanisms for generating genetic diversity within a population.

**Fill in the Blank**
34. The process of making an RNA copy of a gene is called ________.
35. A cell’s ________ remains constant whereas its phenotype changes in response to environmental influences.
36. The enzyme responsible for relaxing supercoiled DNA to allow for the initiation of replication is called ________.
37. Unidirectional replication of a circular DNA molecule like a plasmid that involves nicking one DNA strand and displacing it while synthesizing a new strand is called ________.
38. A ________ mRNA is one that codes for multiple polypeptides.
39. The protein complex responsible for removing intron-encoded RNA sequences from primary transcripts in eukaryotes is called the ________.
40. The third position within a codon, in which changes often result in the incorporation of the same amino acid into the growing polypeptide, is called the ________.
41. The enzyme that adds an amino acid to a tRNA molecule is called ________.
42. A chemical mutagen that is structurally similar to a nucleotide but has different base-pairing rules is called a ________.
43. The enzyme used in light repair to split thymine dimers is called ________.
44. The phenotype of an organism that is most commonly observed in nature is called the ________.
45. A small DNA molecule that has the ability to independently excise from one location in a larger DNA molecule and integrate into the DNA elsewhere is called a ________.
46. ________ is a group of mechanisms that allow for the introduction of genetic material from one organism to another organism within the same generation.
47. The DNA sequence, to which repressors may bind, that lies between the promoter and the first structural gene is called the ________.
48. The prevention of expression of operons encoding substrate use pathways for substrates other than glucose when glucose is present is called ________.

**Short Answer**
49. Can two observably different cells have the same genotype? Explain.
50. Why is primase required for DNA replication?
51. What is the role of single-stranded binding protein in DNA replication?
52. Below is a DNA sequence. Envision that this is a section of a DNA molecule that has separated in preparation for replication, so you are only seeing one DNA strand. Construct the complementary DNA sequence (indicating 5’ and 3’ ends).

DNA sequence: 3’-T A C T G A C T G A C G A T C-5’

53. What is the purpose of RNA processing in eukaryotes? Why don’t prokaryotes require similar processing?

54. Below is a DNA sequence. Envision that this is a section of a DNA molecule that has separated in preparation for transcription, so you are only seeing the antisense strand. Construct the mRNA sequence transcribed from this template.

Antisense DNA strand: 3’-T A C T G A C T G A C G A T C-5’

55. Why does translation terminate when the ribosome reaches a stop codon? What happens?

56. How does the process of translation differ between prokaryotes and eukaryotes?

57. What is meant by the genetic code being nearly universal?

58. Below is an antisense DNA sequence. Translate the mRNA molecule synthesized using the genetic code, recording the resulting amino acid sequence, indicating the N and C termini.

Antisense DNA strand: 3’-T A C T G A C T G A C G A T C-5’

59. Why is it more likely that insertions or deletions will be more detrimental to a cell than point mutations?

60. Briefly describe two ways in which chromosomal DNA from a donor cell may be transferred to a recipient cell during the process of conjugation.

61. Describe what happens when a nonsense mutation is introduced into the gene encoding transposase within a transposon.

62. What are two ways that bacteria can influence the transcription of multiple different operons simultaneously in response to a particular environmental condition?

Critical Thinking

63. A pure culture of an unknown bacterium was streaked onto plates of a variety of media. You notice that the colony morphology is strikingly different on plates of minimal media with glucose compared to that seen on trypticase soy agar plates. How can you explain these differences in colony morphology?

64. Review Figure 11.4 and Figure 11.5. Why was it important that Meselson and Stahl continue their experiment to at least two rounds of replication after isotopic labeling of the starting DNA with $^{15}$N, instead of stopping the experiment after only one round of replication?

65. If deoxyribonucleotides that lack the 3’-OH groups are added during the replication process, what do you expect will occur?

66. Predict the effect of an alteration in the sequence of nucleotides in the –35 region of a bacterial promoter.
67. Label the following in the figure: ribosomal E, P, and A sites; mRNA; codons; anticodons; growing polypeptide; incoming amino acid; direction of translocation; small ribosomal unit; large ribosomal unit.

68. Prior to the elucidation of the genetic code, prominent scientists, including Francis Crick, had predicted that each mRNA codon, coding for one of the 20 amino acids, needed to be at least three nucleotides long. Why is it not possible for codons to be any shorter?

69. Below are several DNA sequences that are mutated compared with the wild-type sequence: 3'-T A C T G A C T G A C G A T C-5'. Envision that each is a section of a DNA molecule that has separated in preparation for transcription, so you are only seeing the template strand. Construct the complementary DNA sequences (indicating 5’ and 3’ ends) for each mutated DNA sequence, then transcribe (indicating 5’ and 3’ ends) the template strands, and translate the mRNA molecules using the genetic code, recording the resulting amino acid sequence (indicating the N and C termini). What type of mutation is each?

   Mutated DNA Template Strand #1: 3'-T A C T G T C T G A C G A T C-5'
   Complementary DNA sequence:
   mRNA sequence transcribed from template:
   Amino acid sequence of peptide:
   Type of mutation:

   Mutated DNA Template Strand #2: 3'-T A C G G A C T G A C G A T C-5'
   Complementary DNA sequence:
   mRNA sequence transcribed from template:
   Amino acid sequence of peptide:
   Type of mutation:

   Mutated DNA Template Strand #3: 3'-T A C T G A C T G A C T A T C-5'
   Complementary DNA sequence:
   mRNA sequence transcribed from template:
   Amino acid sequence of peptide:
   Type of mutation:

   Mutated DNA Template Strand #4: 3'-T A C G A C T G A C T A T C-5'
   Complementary DNA sequence:
   mRNA sequence transcribed from template:
   Amino acid sequence of peptide:
   Type of mutation:

70. Why do you think the Ames test is preferable to the use of animal models to screen chemical compounds for mutagenicity?
The following figure is from Monod’s original work on diauxic growth showing the growth of *E. coli* in the simultaneous presence of xylose and glucose as the only carbon sources. Explain what is happening at points A–D with respect to the carbon source being used for growth, and explain whether the xylose-use operon is being expressed (and why). Note that expression of the enzymes required for xylose use is regulated in a manner similar to the expression of the enzymes required for lactose use.
Appendix 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 A1). 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 A1](image)

**Figure A1**  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 (\(^{12}\text{C}\)), 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 (\(^{13}\text{C}\)) (1.1% of all carbon). [3] \(^{13}\text{C}\) has a mass number of 13 (6 protons + 7 neutrons). Since the atomic number of \(^{13}\text{C}\) is 6, it is still the element carbon; however, it has more mass than the more common form of the element, \(^{12}\text{C}\), because of the extra neutron in the nucleus. Carbon-14 (\(^{14}\text{C}\)) (0.0001% of all carbon) [4] is an example of a radioisotope. \(^{14}\text{C}\) has a mass number of 14 (6 protons + 8 neutrons); however, the extra neutrons in \(^{14}\text{C}\) 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, \(\text{H}_2\text{O}\), 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

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3. ibid.
4. ibid.
together by covalent bonds (Figure A2). 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 H₂O. 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 A2). 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 A2).
Figure A2  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 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 A2).

**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 A1 lists some cations and anions that commonly occur in microbiology. Note that this table includes monoatomic as well as polyatomic ions.

<table>
<thead>
<tr>
<th>Cations</th>
<th>Anions</th>
</tr>
</thead>
<tbody>
<tr>
<td>sodium</td>
<td>Na⁺</td>
</tr>
<tr>
<td>hydrogen</td>
<td>H⁺</td>
</tr>
<tr>
<td>potassium</td>
<td>K⁺</td>
</tr>
<tr>
<td>ammonium</td>
<td>NH₄⁺</td>
</tr>
<tr>
<td>copper (I)</td>
<td>Cu⁺</td>
</tr>
<tr>
<td>copper (II)</td>
<td>Cu²⁺</td>
</tr>
<tr>
<td>iron (II)</td>
<td>Fe²⁺</td>
</tr>
<tr>
<td>iron (III)</td>
<td>Fe³⁺</td>
</tr>
<tr>
<td>nitrate</td>
<td>NO₂⁻</td>
</tr>
<tr>
<td>nitrate</td>
<td>NO₃⁻</td>
</tr>
<tr>
<td>peroxide</td>
<td>O₂²⁻</td>
</tr>
<tr>
<td>phosphate</td>
<td>PO₄³⁻</td>
</tr>
<tr>
<td>pyrophosphate</td>
<td>P₂O₇⁴⁻</td>
</tr>
<tr>
<td>sulfite</td>
<td>SO₃²⁻</td>
</tr>
<tr>
<td>thiosulfate</td>
<td>S₂O₃²⁻</td>
</tr>
</tbody>
</table>

**Table A1**
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\(_6\)H\(_{12}\)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\(_6\)H\(_{12}\)O\(_6\) (*Figure A3*), is calculated as:

- mass of carbon = \(12 \, \text{amu} \times 6 \, \text{atoms} = 72 \, \text{amu}\)
- mass of hydrogen = \(1 \, \text{amu} \times 12 \, \text{atoms} = 12 \, \text{amu}\)
- mass of oxygen = \(16 \, \text{amu} \times 6 \, \text{atoms} = 96 \, \text{amu}\)
- molecular mass of glucose = \(72 \, \text{amu} + 12 \, \text{amu} + 96 \, \text{amu} = 180 \, \text{amu}\)

*Figure A3* 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 (H₂O₂). The reactant hydrogen peroxide is broken down into water, containing one oxygen atom bound to two hydrogen atoms (H₂O), and oxygen, which consists of two bonded oxygen atoms (O₂). 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.

\[
2\text{H}_2\text{O}_2(\text{hydrogen peroxide}) \rightarrow 2\text{H}_2\text{O}(\text{water}) + \text{O}_2(\text{oxygen})
\]

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:

\[
\text{carbonic anhydrase: } \text{CO}_2 + \text{H}_2\text{O} \rightleftharpoons \text{H}_2\text{CO}_3 \rightleftharpoons \text{H}^+ + \text{HCO}_3^-
\]

**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 \(\delta^+\) on each hydrogen atom and two \(\delta^-\) 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.
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 A4** 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 A5**). 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.
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 archaean 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, \( \text{pH} = -\log_{10}[H^{+}] \). 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 A6). 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 A6](http://cnx.org/content/col12087/1.4)

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\(^{+}\)].
Appendix 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”):

\[ 5^2 = 5 \times 5 = 25 \]

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:

\[ 5^3 = 5 \times 5 \times 5 = 125 \]

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:

\[ n^x = n \times n^{x-1} \]

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.

\[ 25\% = \frac{25}{100} = \frac{1}{4} \]

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.

\[ 10\% = \frac{10}{100} = 0.10 \]

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.

\[ 0.833 = \frac{833}{1000} = \frac{83.3}{100} = 83.3\% \]

To convert a fraction to a percent, first convert the fraction to a decimal, and then convert the decimal to a percent.

\[ \frac{3}{4} = 0.75 = \frac{75}{100} = 75\% \]

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.

\[ \frac{\text{carriers}}{\text{total students}} = \frac{15}{23} \]

Then divide the numerator by the denominator.

\[ \frac{15}{23} = 15 \div 23 \approx 0.65 \]
Finally, to convert a decimal to a percent, multiply by 100.

\[ 0.65 \times 100 = 65\% \]

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.

\[ \text{positive + negative} = 9 + 28 = 37 \]

The whole sample consisted of 37 students. The fraction of positives is:

\[ \frac{\text{positive}}{\text{total students}} = \frac{9}{37} \]

To find the percent of students who are carriers, divide the numerator by the denominator and multiply by 100.

\[ \frac{9}{37} = 9 \div 37 \approx 0.24 \]

\[ 0.24 \times 100 = 24\% \]

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:

\[ \frac{9}{37} = \frac{x}{100} \]

Now, cross multiply and solve for the unknown:

\[ 9 \times 100 = 37x \]

\[ \frac{9 \times 100}{37} = x \quad \text{Divide both sides by 37} \]

\[ \frac{900}{37} = x \quad \text{Multiply} \]

\[ 24 \approx x \quad \text{Divide} \]

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.

\[ 1.9436(10) = 19.436 \]

\[ 1.9436(100) = 194.36 \]

\[ 1.9436(1000) = 1943.6 \]

The number of places that the decimal point moves is the same as the number of zeros in the power of ten. **Table B1** summarizes the results.

<table>
<thead>
<tr>
<th>Multiply by</th>
<th>Zeros</th>
<th>Decimal point moves . . .</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>1</td>
<td>1 place to the right</td>
</tr>
<tr>
<td>100</td>
<td>2</td>
<td>2 places to the right</td>
</tr>
<tr>
<td>1,000</td>
<td>3</td>
<td>3 places to the right</td>
</tr>
<tr>
<td>10,000</td>
<td>4</td>
<td>4 places to the right</td>
</tr>
</tbody>
</table>

**Table B1**
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.

\[
\begin{align*}
1.9436 \div 10 &= 0.19436 \\
1.9436 \div 100 &= 0.019436 \\
1.9436 \div 1000 &= 0.0019436 \\
\end{align*}
\]

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 B2.

<table>
<thead>
<tr>
<th>Standard Notation</th>
<th>Scientific Notation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1000</td>
<td>$1 \times 10^3$</td>
</tr>
<tr>
<td>100</td>
<td>$1 \times 10^2$</td>
</tr>
<tr>
<td>10</td>
<td>$1 \times 10^1$</td>
</tr>
<tr>
<td>1</td>
<td>$1 \times 10^0$</td>
</tr>
<tr>
<td>0.1</td>
<td>$1 \times 10^{-1}$</td>
</tr>
<tr>
<td>0.01</td>
<td>$1 \times 10^{-2}$</td>
</tr>
</tbody>
</table>

Table B2

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 $0.00000000036 = 3.6 \times 10^{-10}$.

**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

and

0.123 = 1.23 \times 0.1 = 1.23 \times 10^{-1}

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 B3.

<table>
<thead>
<tr>
<th>Number</th>
<th>Exponential Form</th>
<th>Common Logarithm</th>
</tr>
</thead>
<tbody>
<tr>
<td>1000</td>
<td>(10^3)</td>
<td>3</td>
</tr>
<tr>
<td>10</td>
<td>(10^1)</td>
<td>1</td>
</tr>
<tr>
<td>1</td>
<td>(10^0)</td>
<td>0</td>
</tr>
<tr>
<td>0.1</td>
<td>(10^{-1})</td>
<td>-1</td>
</tr>
<tr>
<td>0.001</td>
<td>(10^{-3})</td>
<td>-3</td>
</tr>
</tbody>
</table>

Table B3

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.

\[
\begin{align*}
4.383 \text{ g} \\
3.0021 \text{ g} \\
7.385 \text{ g}
\end{align*}
\]

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.

\[
0.638 \frac{\text{g}}{\text{mL}} \times 6.6 \text{ mL} = 4.1 \text{ g}
\]

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,

\[
N_i = N_0 \times 2^j
\]

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:

\[
N_i = N_0 \times 2^j \\
N_{90} = 4 \times 2^3 \\
N_{90} = 4 \times 8 = 32
\]

The number of cells after 90 minutes is 32.

**Most Probable Number**

The table in Figure B1 contains values used to calculate the most probable number example given in How Microbes Grow.
## Most Probable Number Table

<table>
<thead>
<tr>
<th>Number of tubes giving a positive reaction for a 5-tube set</th>
<th>MPN (per 100 ml)</th>
<th>95% Confidence Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 ml</td>
<td>1 ml</td>
<td>0.1 ml</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
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**Figure B1**
Appendix C

Glossary

454 sequencing (pyrosequencing) a next generation sequencing technique in which fragmented DNA has DNA adapters attached, is amplified by PCR, is attached to a bead, and then placed into a well with sequencing reagents, and the flash of light produced by the release of pyrophosphate on addition of a nucleotide is monitored

5' cap methylguanosine nucleotide added to 5' end of a eukaryotic primary transcript

70S ribosome a ribosome composed of 50S and 30S subunits

80S ribosome cytoplasmic eukaryotic ribosome composed of 60S and 40S subunits

A

α-helix secondary structure consisting of a helix stabilized by by hydrogen bonds between nearby amino acid residues in a polypeptide

A (aminocyl) site functional site of an intact ribosome that binds incoming charged aminocyl tRNAs

A-B exotoxin class of exotoxin that contains A subunits, which enter the cell and disrupt cellular activities, and B subunits, which bind to host cell receptors

ABO blood group system set of glycoprotein antigens found on the surface of red blood cells; the presence or absence of specific carbohydrates determines blood type

absorbance when a molecule captures energy from a photon and vibrates or stretches, using the energy

Acinetobacter baumannii a condition characterized by damage to the cornea and possible blindness caused by parasitic infection of the protozoan Acanthamoeba

acelluar not made of cells

acid-fast stain a stain that differentiates cells that have waxy mycolic acids in their gram-positive cell walls

acidic dye a chromophore with a negative charge that attaches to positively charged structures

acidophile organism that grows optimally at a pH near 3.0

acne a skin disease in which hair follicles or pores become clogged, leading to the formation of comedones and infected lesions

acquired immunodeficiency syndrome (AIDS) disease caused by HIV, characterized by opportunistic infections and rare cancers

actin a protein that polymerizes to form microfilaments

activation energy needed to form or break chemical bonds and convert a reactant or reactants to a product or products

activator protein that increases the transcription of a gene in response to an external stimulus

active carrier an infected individual who can transmit the pathogen to others regardless of whether symptoms are currently present

active immunity stimulation of one’s own adaptive immune response

active site location within an enzyme where substrate(s) bind

acute disease disease of a relatively short duration that develops and progresses in a predictable pattern

acute glomerulonephritis inflammation of the glomeruli of the kidney, probably resulting from deposition of immune complexes and an autoimmune response caused by self-immune mimicry by a pathogen

acute necrotizing ulcerative gingivitis a severe form of gingivitis, also called trench mouth

acute otitis media inflammatory disease of the middle ear resulting from a microbial infection

acute rheumatic fever sequelae of streptococcal pharyngitis; comorbidities include arthritis and carditis

acute-phase proteins antimicrobial molecules produced by liver cells in response to pathogen-induced stimulation events

acyclovir antiviral guanosine analog; inhibits DNA replication

adaptive immunity third-line defense characterized by specificity and memory

Addison disease autoimmune disease affecting adrenal gland function

adenine purine nitrogenous base found in nucleotides

adenosine diphosphate (ADP) nucleotide derivative and relative of ATP containing only one high-energy phosphate bond

adenosine monophosphate (AMP) adenosine molecule bonded to a ribose molecule and to a single phosphate group, having no high-energy phosphate bonds

adenosine triphosphate (ATP) energy currency of the cell; a nucleotide derivative that safely stores chemical energy in its two high-energy phosphate bonds

adhesins molecules on the surface of pathogens that promote colonization of host tissue

adhesion the capability of microbes to attach to host cells

aerobic respiration use of an oxygen molecule as the final electron acceptor of the electron transport system

aerotolerant anaerobe organism that does not use oxygen but tolerates its presence

affinity maturation function of the immune system by which B cells, upon re-exposure to antigen, are selected to produce higher affinity antibodies

affinity measure of how tightly an antibody-binding site binds to its epitope

aflatoxin chemical produced by the fungus Aspergillus flavus; both a toxin and the most potent known natural carcinogen

African sleeping sickness see human African trypanosomiasis

agaroal gel electrophoresis a method for separating populations of DNA molecules of varying sizes by differential migration rates caused by a voltage gradient through a horizontal gel matrix

agglutination binding of different pathogen cells by Fab regions of the same antibody to aggregate and enhance elimination from body

glycals buildup of leukocytes that lack granules in the cytoplasm

alarmone small intracellular derivative of a nucleotide that signals a global bacterial response (i.e., activating a regulon of operons) to an environmental stress

albendazole an antihelminthic drug of the benzimidazole class that binds to helminthic β-tubulin, preventing microtubule formation

algae (singular: alga) any of various unicellular and multicellular photosynthetic eukaryotic organisms; distinguished from plants by their lack of vascular tissues and organs

alkaliphile organism that grows optimally at pH above 9.0

amphatic having two flagella or tufts of flagella, with one flagellum or tuft located at each end of the bacterial cell

amphotericin B antifungal drug of the polycyclic class that is used to treat several systemic fungal infections

amplitude the height of a wave

anabolism chemical reactions that convert smaller molecules into more complex ones

anaerobe chamber closed compartment used to handle and grow obligate anaerobic cultures

anaerobe jar container devoid of oxygen used to grow obligate anaerobes

anaerobic respiration use of a non-oxygen inorganic molecule, like CO2, nitrate, nitrite, oxidized iron, or sulfate, as the final electron acceptor at the end of the electron transport system

analytical epidemiology study of disease outbreaks to establish associations between an agent and a disease state through observational studies comparing groups of individuals

anaphylactic shock another term for anaphylaxis

anaphylaxis systemic and potentially life-threatening type I hypersensitivity reaction

anergy peripheral tolerance mechanism that prevents self-reactive T cells from being activated by self-antigens through lack of co-stimulation

annealing formation of hydrogen bonds between the nucleotide base pairs of two single-stranded complementary nucleic acid sequences
anoxic photosynthesis type of photosynthesis found in many photosynthetic bacteria, including the purple and green bacteria, where an electron donor other than H₂ is used to replace an electron lost by a reaction center pigment, resulting no oxygen production

antrax disease caused by Bacillus anthracis, the cutaneous form causes a skin lesion to develop; gastrointestinal and inhalation antrax have high mortality rates

antibiogram compilation of the antimicrobial susceptibilities recorded for local bacterial strains, which is useful for monitoring local trends in antimicrobial resistance and aiding the prescription of appropriate empiric antibacterial therapy

antibiotic-associated diarrhea diarrhea that develops after antibiotic treatment as a result of disruption to the normal microbiota; C. difficile is a particularly serious example

antibody screen test to make sure that a potential blood recipient has not produced antibodies to antigens other than the ABO and Rh antigens

antibody Y-shaped glycoprotein molecule produced by B cells that binds to specific epitopes on an antigen

antibody-dependent cell-mediated cytotoxicity (ADCC) mechanism by which large pathogens are marked for destruction by specific antibodies and then killed by secretion of cytotoxins by natural killer cells, macrophages, or eosinophils

anticond three-nucleotide sequence of a mature tRNA that interacts with an mRNA codon through complementary base pairing

antigen (also, immunogen) a molecule that stimulates an adaptive immune response

antigenic able to stimulate an adaptive immune response

antigenic drift form of slight antigenic variation that occurs because of point mutations in the genes that encode surface proteins

antigenic shift form of major antigenic variation that occurs because of gene reassortment

antigenic changing of surface antigens (carbohydrates or proteins) such that they are no longer recognized by the host’s immune system

antigen-presenting cells (APC) macrophages, dendritic cells, and B cells that process and present foreign pathogen antigens for the purpose of activating T cells and adaptive immune defenses

antimicrobial drugs compounds that are competitive inhibitors for bacterial metabolic enzymes

antimicrobial drugs chemical compounds, including naturally produced drugs, semisynthetic derivatives, and synthetic compounds, that target specific microbial structures and enzymes, killing specific microbes or inhibiting their growth

antimicrobial peptides (AMPs) class of nonpeptide antimicrobial peptides with broad-spectrum antimicrobial properties

antiparallel two strands of DNA helix oriented in opposite directions; one strand is oriented in the 5’ to 3’ direction, while the other is oriented in the 3’ to 5’ direction

antisense RNA small noncoding RNA molecules that inhibit gene expression by binding to mRNA transcripts via complementary base pairing

antisense strand transcription template strand of DNA, the strand that is transcribed for gene expression

antisepsis protocol that removes potential pathogens from living tissue

antiseptic antimicrobial chemical that can be used safely on living tissue

antiserum serum obtained from an animal containing antibodies against a particular antigen that was previously introduced to the animal

aeroenzyme enzyme without its cofactor or coenzyme

apoptosis programmed and organized cell death without lysis of the cell

arachnoid mater middle meningeal membrane surrounding the brain that produces cerebrospinal fluid

arboviral encephalitis infection by an arthropod-borne virus that results in an inflammation of the brain

arbovirus any of a variety of viruses that are transmitted by arthropod vectors

archaea any of various unicellular prokaryotic microorganisms, typically having cell walls containing pseudopeptidoglycan

Archea domain of life separate from the domains Bacteria and Eukarya

antiretroviral treatment effective against HIV that is thought to increase intracellular levels of reactive oxygen species in target microbes

terery large, thick-walled vessel that carries blood from the heart to the body tissues

Arthus reaction localized type III hypersensitivity

artificial active immunity immunity acquired through exposure to pathogen and pathogen antigens through a method other than natural infection

artificial passive immunity transfer of antibodies produced by a donor to another individual for the purpose of preventing or treating disease

arcsarisation soil-transmitted intestinal infection caused by the large nematode roundworm Ascaris lumbricoides

ascocarpasexual stage of fungi bearing spores

ascorpoe axenial spore produced by ascus and ascospores

ascus structure of ascocarp containing spores

aspxis sterile state resulting from proper use of microbial control protocols

asptic technique method or protocol designed to prevent microbial contamination of sterile objects, locations, or tissues

aspartylgllsis fungal infection caused by the mold Aspergillus; immunocompromised patients are primarily at risk

asymptomatic carrier an infected individual who exhibits no signs or symptoms of disease yet is capable of transmitting the pathogen to others

asymptomatic not exhibiting any symptoms of disease

atomic force microscope a scanning probe microscope that uses a thin probe that is passed just through the surface of an object to map its topography

ATP synthase integral membrane protein that harnesses the energy of the proton motive force by allowing hydrogen ions to diffuse down their electrochemical gradient, causing components of this protein to spin, making ATP from ADP and Pᵢ

attachment binding of phage or virus to host cell receptors

attenuation regulatory system of prokaryotes whereby secondary subunit structures formed within the 5’ end of an mRNA can be transcribed determine both if transcription to complete the synthesis of this mRNA will occur and if this mRNA will be used for translation

autochthon specialized device for the moist-heat sterilization of materials through the application of pressure to steam to reach temperatures above the boiling point of water

autocline functions to a cytokine signal released from a cell to a receptor on its own surface

autograft tissue transplanted from a location on an individual to a different location on the same individual

autoimmune disease loss of tolerance to self, resulting in immune-mediated destruction of self cells and tissues

autologous signaling molecule produced by a bacterial cell that can modify the activity of surrounding cells; associated with quorum sensing

autoruscopy the method of producing a photographic image from radioactive decay; in molecular genetics the method allows the visualization of radioactively-labeled DNA probes that have hybridized to a nucleic acid sample

auxotroph organisms that have a nutritional requirement in a gene encoding the biosynthesis of a specific nutrient such as an amino acid

avidity strength of the sum of the interactions between an antibody and antigen

axon long projection of a neuron along which an electrochemical signal is transmitted

azithromycin semisynthetic macrolide with increased spectrum of activity, decreased toxicity, and increased half-life compared with erythromycin

B beta-lactamases bacterially produced enzymes that cleave the β-lactam ring of susceptible β-lactam antimicrobials, rendering them inactive and confering resistance

β-lactams group of antimicrobials that inhibit cell wall synthesis; includes the penicillins, cephalosporins, carbapenems, and monobactams; inhibits the transpeptidase cross-linking activity of penicillin-binding proteins

β-oxidation process of fatty acid degradation that sequentially removes two-carbon units from fatty acids, producing NADH and FADH₂, entry into the Krebs cycle

β-pleated sheet secondary structure consisting of pleats formed by hydrogen bonds between localized segments of amino acid residues on the backbone of the polypeptide chain

B cell receptors (BCRs) membrane-bound IgD and IgM antibody that bind specific antigen epitopes with Fab antigen-binding region

B lymphotoxy-producing cells of humoral immunity; B cell

babesiosis tickborne protozoan infection caused by Babesia spp. and characterized by malaise, fatigue, fever, headache, myalgia, and joint pain

bacillary dysentery gastrointestinal illness caused by Shigella bacteria, also called shigellosis

bacillus (bacilli) rod-shaped prokaryotic cell

bacitracin group of structurally similar peptides that block the movement of peptidoglycan precursors across the cell membrane, inhibiting peptidoglycan synthesis

bacteremia condition marked by the presence of bacteria in the blood

bacteriophage singular: bacterium) any of various unicellular prokaryotic microorganisms typically (but not always) having cell walls that contain peptidoglycan

bacterial lawn confluent bacterial growth on an agar plate

bacterial meningitis bacterial infection that results in an inflammation of the meninges

bacterial vaginosis a condition caused by an overgrowth of bacteria in the vagina that may or may not cause symptoms

bactericidal irreversible inhibition of a microbe’s ability to divide

bactericide chemical or physical treatment that kills bacteria

bacteriophages green, purple, or blue pigments of bacteria; they are similar to chlorophyll of plants

bacteriology the study of bacteria

bacteriophage virus that infects bacteria

bacteriostatic having the ability to inhibit bacterial growth, generally by means of chemical or physical treatment; reversible inhibition of a microbe’s ability to divide

barophile organism that grows under high atmospheric pressure

basal body component of flagella flagellum or cilium composed of nine microtubule triplets and attaches the flagellum or cilium to the cell

base sequence identity of the specific nucleotides present in a nucleic acid strand and their order within the strand

basis cey chromophore with a positive charge that attaches to negatively charged structures

basidium (basidiom, sing.) small club-shaped structures of basidiomycete fungi where basidiospores are produced
cerebrospinal fluid (CSF) sterile liquid produced in the brain that fills the subarachnoid space of the brain and spinal column

cervix the part of the uterus that connects to the vagina

cFB group phylum consisting of the gram-negative, rod-shaped nonproteobacteria genera Cytophaga, Flexibacter, and Bacteroides

Chagas disease potentially fatal protozoan infection caused by Trypanosoma cruzi and endemic to Central and South America; transmitted by the triatomin bug (kissing bug) chancroid an STI caused by Haemophilus ducreyi that produces soft chancres on genitals

clostridiosis characterized by severe diarrhea

codominant characterized by two separate copies of the same gene, each of which is expressed

codon three-nucleotide sequence within mRNA that specifies a particular amino acid to be incorporated into the polypeptide being synthesized
congenital common childhood disease caused by the varicella-zoster virus and marked by the formation of pustular lesions on the trunk

congenital chlamydia a common STI caused by Chlamydia trachomatis

congenital chloramphenicol protein synthesis inhibitor with broad-spectrum activity that binds to the 50S subunit, inhibiting peptide bond formation
congenital chlorophyll a type of photosynthetic pigment found in plants and blue-green algae

congenital chloroplast organelle found in plant and algal cells in which photosynthesis occurs

Cholera gastrointestinal illness caused by Vibrio cholerae characterized by severe diarrhea

cholinergic transmission of nerve impulses across the synapse that is mediated by acetylcholine

Chromalveolata phylum consisting of the gram-negative, chloroplast-containing eukaryotes

Chromatin combination of DNA with RNA binding proteins

chromogenic substrate colorless substrate (chromogen) that is converted into a colored end product by the enzyme

chromophores pigments that absorb and reflect particular wavelengths of light (giving them a color)

chromosome discrete DNA structure within a cell that controls cellular activities

chronic any disease that progresses and persists over a long time

chronic granulomatous disease primary immunodeficiency caused by an impaired ability of phagocytic cells to kill ingested bacteria in the phagolysosome

chronic wasting disease prion disease of deer and elk in the United States and Canada

cilia (singular: cilium) short, filamentous structures found on some eukaryotic cells; each is composed of microtubules in a 9 + 2 array, and may be used for locomotion, feeding, and/or movement of extracellular particles that come in contact with the cell
ciliated epithelial cells hair-like cells in the respiratory tract that beat, pushing mucus secretions and trapped debris away from the sensitive tissues of the lungs

ciliates protozoa with cilia (Ciliophora), including Paramecium and Stentor, classified within the Chromalveolata

cisterna the sacs of the endoplasmic reticulum

citrin cycle see Krebs cycle

class switching gene reorganization of constant region gene segments in plasmid cccDNA to switch antibody production from IgM to IgG, IgA, or IgE

clinically see clinical

clonal a genetically identical cell or individual

clostridium perfringens gastroenteritis relatively mild gastrointestinal illness caused by C. perfringens

clotho gene that controls cellular activities

colchicine anticancer drug that disrupts microtubules and inhibits cell division

collagen enzyme that digests collagen, the dominant protein in connective tissue

Colitis inflammation of the large intestine

Colonic enteric motor control network mechanism of horizontal gene transfer in bacteria in which DNA is directly transferred from one bacterial cell to another by a conjugation pilus

Colony the microscopic specimen of a cultured organism that is visible to the naked eye

Colonization mechanism of horizontal gene transfer in bacteria in which DNA is directly transferred from one bacterial cell to another by a conjugation pilus

colonial epithelium tissue, and sites of inflammation

complement fixation test test for antibodies against a specific pathogen using complement-mediated hemolysis

complement system series of proteins that can become activated in the presence of invading microbes, resulting in opsonization, inflammation, and lysis of pathogens

complementary base pairs pairs pairing due to hydrogen bonding that occurs between a specific purine and a specific pyrimidine; A bonds with T (in DNA), and C bonds with G

complementary DNA (cDNA) a DNA molecule complementary to mRNA that is made through the activity of reverse transcriptase

complex media media that contain extracts of animals and plants that are not chemically defined

complex virus virus shape that often includes intricate characteristics not seen in the other categories of capsid

compound microscope a microscope that uses multiple lenses to focus light from the specimen

condenser lens a lens on a microscope that focuses light from the light source onto the specimen

conditional mutation mutant form of a gene whose mutant phenotype is expressed only under certain environmental conditions

confluent growth when cells become crowded and overlap, preventing further division

cone scanning laser microscope that uses fluorescent dyes and excitation lasers to create three-dimensional images

coriolism see cyclin

correlate to see correlation

corticosteroid hormone produced by the adrenal cortex

cotransporter mechanism of horizontal gene transfer in bacteria in which DNA is directly transferred from one bacterial cell to another by a conjugation pilus

cranial nerves cranial nerves that carry sensation and voluntary movement between the brain and body

craspous development of a thorny plant leaf

crescent new moon

crocidolite asbestos mineral with a fibrous structure

crohn's disease inflammatory bowel disease

C. perfringens mild gastrointestinal illness caused by Clostridium perfringens

crohn's disease infectious fungal pathogen

cryptic genes genes that are not expressed at all in the cell

dNA, and C bonds with G, T with A, and G with C base pairing due to hydrogen bonding between homopurines and homopyrimidines and complementary base pairing between heteropurines and pyrimidines

dna polymerase enzyme that catalyzes the synthesis of DNA from nucleoside triphosphate substrates

dna sequencing method for determining the sequence of the nucleotides in a DNA molecule

dna virus a virus that is composed of a DNA genome and either RNA or DNA as its genetic material

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dna virus a virus that is composed of a DNA genome and either RNA or DNA as its genetic material
cooperative interactions interactions between populations in which both benefit
cortex tightly packed layer of fungal filaments at the outer surface of a lichen; foliose lichens have a second cortex layer beneath the medulla
counterstain a secondary stain that adds contrasting color to tissues from which the primary stain has been washed out by a decolorizing agent
creation shriveling of a cell
Creutzfeldt–Jakob disease form of transmissible spongiform encephalopathy found in humans; typically a fatal disease
crisis phase stage at which a fever breaks, reaching a peak before the hypothalamus resets back to normal body temperature
critical item object that must be sterile because it will be used inside the body, often penetrating sterile tissues or the bloodstream
cross-match in the major cross-match, donor red blood cells are checked for agglutination using recipient serum; in the minor cross-match, donor serum is checked for agglutinating antibodies against recipient red blood cells
cross-presentation a mechanism by which dendritic cells process antigens for MHC I presentation to CD8 T cells, cells process antigens for MHC I presentation to CD8 T cells through phagocytosis of the pathogens (which would normally lead to MHC II presentation)
cross-resistance when a single resistance mechanism confers resistance to multiple antimicrobial drugs
cross-sectional study a type of observational study in which measurements are made on cases, both affected and unaffected, at one point in time and the measurements are analyzed to uncover associations with the disease state
crustose lichens lichens that are tightly attached to the substrate, giving them a crumple appearance
cryptococcosis fungal pneumonia caused by the encapsulated yeast Cryptococcus neoforans commonly found in bird droppings
cryptosporidiosis intestinal infection caused by Cryptosporidium parvum or C. hominis
culture density the number of cells per volume of broth
culture medium combination of compounds in solution that supports growth
cutaneous mycosis any fungal infection that affects the surface of the skin, hair, or nails
cyanoacteria phototropic, chlorophyll-containing bacteria that produce large amounts of gaseous oxygen
cyclic AMP (cAMP) intracellular signaling molecule made through the action of adenyl cyclase from ATP when glucose levels are low, with the ability to bind to a catalytic activator protein to allow it to bind to regulatory regions and activate the transcription of operons encoding enzymes for metabolism of alternative substrates
cyclic photophosphorylation pathway used in photosynthetic organisms when the cell’s need for ATP outweighs that for NADPH, thus bypassing NADPH production
cyclopia intestinal infection caused by Cyclospora cayetanensis
cytisic echinococcosis hydatid disease, an infection caused by the tapeworm Echinococcus granulosus that can cause cyst formation
cysticeri larval form of a tapeworm

cystitis inflammation of the bladder
cysts microbial cells surrounded by a protective outer covering; some microbial cysts are formed to help the microbe survive harsh conditions, whereas others are a normal part of the life cycle
cytochrome oxidase final ETS complex used in others are a normal part of the life cycle to help the microbe survive harsh conditions, whereas others are a normal part of the life cycle
cytokine storm an excessive release of cytokines, typically triggered by a superantigen, that results in unregulated activation of T cells
cytokines protein molecules that act as a chemical signals; produced by cells in response to a stimulation event
cytomegalovirus (CMV) infection human herpesvirus 5 infection that is typically asymptomatic but can become serious in immunocompromised patients, transplant recipients, and developing fetuses
cytopathic effect cell abnormality resulting from a viral infection
cytoplasm the gel-like material composed of water and dissolved or suspended chemicals contained within the plasma membrane of a cell
cytomatic membrane see cell membrane
cytoprotect a protozoan cell structure that is specialized for excretory functions
cystine pyrimidine nitrogenous base found in nucleotides
cytoskeleton a network of filaments or tubules in the eukaryotic cell that provides shape and structural support for cells; aids movement of materials throughout the cell
cytoskeleton a network of filaments or tubules in the eukaryotic cell that provides shape and structural support for cells; aids movement of materials throughout the cell
cytotoxic T cells effector cells of cellular immunity that target and eliminate cells infected with intracellular pathogens through induction of apoptosis
cytotoxicity harmful effects to host cell
cystatin a cysteine protease inhibitor
d-acetylcysteine a form of vitamin C
darkfield microscopy a compound light microscope that produces a bright image on a dark background, typically a modified brightfield microscope
defense (phase defense) phase of the growth curve at which the number of dying cells exceeds the number of new cells formed
decimal reduction time (DRT) or D-value amount of time it takes for a specific protocol to produce a one order of magnitude decrease in the number of organisms; that is, death of 90% of the population
decolorizing agent a substance that removes a stain, usually from some parts of the specimen
deleteriously harmful, hazardous, or detrimental to
deeply branching bacteria bacteria that occupy the lowest branches of the phylogenetic tree of life
definitive host the preferred host organism for a parasite, in which the parasite reaches maturity and may reproduce sexually
degeneracy redundancy in the genetic code because a given amino acid is encoded by more than one nucleotide triplet codon
degenerating protocol that significantly reduces microbial numbers by using mild chemicals (e.g., soap) and gentle scrubbing of a small area of skin or tissue to avoid the transmission of pathogenic microbes
degranulation release of the contents of mast cell granules in response to the cross-linking of IgG molecules on the cell surface with allergen molecules
dehydration chemical reaction in which monomer molecules bind end to end in a process that results in the formation of water molecules as a byproduct
deletion type of mutation involving the removal of one or more bases from a DNA sequence
delayed-type hypersensitivity reaction in which monomer molecules bind end to end in a process that results in the formation of water molecules as a byproduct
delayed-type hypersensitivity reaction in which monomer molecules bind end to end in a process that results in the formation of water molecules as a byproduct
denatured protein protein that has lost its secondary and tertiary structures (and quaternary structure, if applicable) without the loss of its primary structure

dendritic cell any macrophage-like cell present in lymphoid tissues of the body

dendritic extensions branched extensions of the soma of a neuron that interact with other cells
dengue fever mosquito-borne viral hemorrhagic disease; also known as breakbone fever
dental calculus calcified heavy plaque on teeth, also called tartar
dental caries cavities formed in the teeth as a result of tooth decay caused by microbial activity
deoxynucleobuic acid (DNA) double-stranded nucleic acid composed of deoxyribonucleotides that serves as the genetic material of the cell
deoxynucleotides DNA nucleotides containing deoxyribose as the pentose sugar component
dermatophyte any fungus of the genera Microsporum, Epidermophyton, or Trichophyton, which feed on keratin (a protein found in skin, hair, and nails) and can cause cutaneous infections
dermis the second layer of human skin, found between the epidermis and the hypodermis
descriptive epidemiology a method of studying a disease outbreak using case histories, contact interviews, medical information, and other sources of information
desensitization injections of antigens that lead to production of antigen-specific IgG molecules, effectively outcompeting IgE molecules on the surface of sensitized mast cells for antigen
desiccation method of microbial control involving the removal of water from cells through drying or dehydration
desquamation peeling and shedding of outermost skin
diabetes process by which leukocytes pass through capillary walls to reach infected tissue; also called extravasation

diaphragm a lock that prevents flow

dihydrotestosterone a hormone produced in the male reproductive system

dilation refers to a process that increases the size of a structure

dimorphic fungus a fungus that can take the form of a yeast or a mold, depending on environmental conditions
diphtheria serious form of the larynx, caused by the toxigenic bacterium Corynebacterium diphtheriae
diploid having two copies of each chromosome

direct agglutination assay assay that can be used to detect the agglutination of bacteria by the action of antibodies in patient serum

direct antihuman globulin test (DAT) another name for a direct Coombs’ test

direct contact transmission movement of a pathogen between hosts by physical contact or transfer in droplets at a distance less than one meter

direct Coombs’ test assay that looks for antibodies in vivo against red blood cells caused by various types of infections, drug reactions, and autoimmune disorders
direct ELISA enzyme-linked immunosorbent assay in which the antigens are immobilized in the well of a microtiter plate; only a single antibody is used in the test
direct fluorescent antibody (DFA) test FA technique in which the labeled antibody binds to the target antigen
direct hemagglutination assay test that determines the titer of certain bacteria and viruses that causes clumping of red blood cells
direct microscopic cell count counting of cells using a calibrated slide under a compound microscope
direct repair (light repair or photoreactivation) light-dependent mechanism for repairing pyrimidine dimers involving the enzyme photolyase

disaccharide one of two monoosaccharides linked together by a glycosidic bond
disease any condition in which the normal structure or function of the body is damaged or impaired
disinfectant antimicrobial chemical applied to a body
infectious disease the釋放 that may be toxic to tissue
disinfection protocol that removes potential pathogens from a host
diffusion method a technique for measuring the effectiveness of one or more antimicrobial agents against a given bacterium; involves measuring the zone(s) of inhibition around the chemical agent(s) in a culture of the bacterium
dispersion the separation of light of different frequencies due to different degrees of refraction
dissulfide bond covalent bond between the sulfur atoms of two cysteine side chains
DNA gyrase (topoisomerase II) bacterial topoisomerase that relaxes the supercoiled chromosome to make DNA more accessible for the initiation of replication
DNA ligase enzyme that catalyzes the formation of a covalent phosphodiester linkage between the 3'-OH end of one DNA fragment and the 5'-phosphate end of another DNA fragment
DNA packaging process in which histones or other DNA-binding proteins perform various levels of DNA wrapping and attachment to scaffolding proteins to allow the DNA to fit inside a cell
DNA polymerase class of enzymes that adds nucleotides to the free 3'-OH group of a growing DNA chain that are complementary to the template strand
DNA primers short, synthetic, single-stranded DNA fragments of known sequence that bind to specific target sequences within a sample due to complementarity between the target DNA sequence and the primer; commonly used in PCR but may be used in other hybridization techniques
DNA probe a single-stranded DNA fragment that is complementary to part of the gene (DNA or RNA) of interest
DNase pathogen-produced nuclease that degrades extracellular DNA
dosage amount of medication given during a certain time interval
double immunodiffusion see Ouchterlony assay
doubling time the time it takes for the population to double; also referred to as generation time
droplet transmission direct contact transmission of a pathogen transferred in sneezed or coughed droplets of mucus that land on the new host within a radius of one meter
drug resistance ability of a microbe to persist and grow in the presence of an antimicrobial drug
dry-heat sterilization protocol that involves the direct application of high heat
dura mater tough, outermost membrane that surrounds the CNS
dynein motor proteins that interact with microtubules in eukaryotic flagella and cilia
dysentery intestinal inflammation that causes diarrhea with blood and mucus
dysuria urination accompanied by burning, discomfort, or pain
ectoplasm outer, more gelatinous layer of cytoplasm under a prokariot cell membrane
edema swelling due to accumulation of fluid and protein in tissue as a result of increased permeability of capillary walls during an inflammatory response; chronic edema can also result from blockage of lymphatic vessels, as in the case of elephantiasis
effector cells activated cells of cellular immunity that are involved in the immediate immune response, primarily to defend the body against pathogens
electron carrier cellular molecule that accepts high-energy electrons from reduced molecules like foods and later serves as an electron donor in subsequent redox reactions
electron microscope a type of microscope that uses short-wavelength electron beams rather than light to increase magnification and resolution
electron transport system (ETS) series of membrane-associated protein complexes and associated mobile accessory electron carriers important in the generation of the proton motive force required for ATP production by chemiosmosis; the last component involved in the cellular respiration of glucose
electroporation a genetic engineering technique in which cells are exposed to a short electric pulse, inducing them to take up DNA molecules from their environment
Elementary bodies metabolically and reproducibly inactive, endosome-like form of intracellular bacteria that spend most of its time outside of cells
elongation in DNA replication stage of DNA replication during which DNA polymerase adds nucleotides complementary to the parental strand, to the 3’ end of a growing DNA strand
elongation in transcription stage of transcription during which RNA polymerase extends the RNA molecule by adding RNA nucleotides, complementary to the template DNA strand
elongation of translation stage of translation during which amino acids are added one by one to the C-terminus of the growing polypeptide
Embden-Meyerhof-Parnas (EMP) pathway type of glycolysis found in animals and the most common in microbes
emerging infectious disease a disease that is new to the human population or has increased in prevalence over the previous 20 years
enantiomers stereoisomers that are mirror images of each other and nonsuperimposable
encephalitis inflammation of the tissues of the brain
encystment the process of forming a cyst
endemic disease an illness that is constantly present (often at low levels) in a population
endergonic reaction chemical reaction that requires energy beyond activation energy to occur
endocarditis inflammation of the endocardium, especially the heart valves
endocrine function refers to a cytokine signal released from a cell and carried by the bloodstream to a distant recipient cell
endotoxicity the uptake of molecules through plasma membrane invagination and vacuole/vesicle formation
endomembrane system a series of organelles (endoplasmic reticulum, Golgi apparatus, lysosomes, and transport vesicles) arranged as membranous tubules, sacs, and disks that synthesize many cell components
endoplasmic reticulum part of the endomembrane system that is an interconnected array of tubules and flattened sacs with a single lipid bilayer that may be either rough or smooth; important in synthesizing proteins and lipids
endoscopy a cellular structure formed by some bacteria in response to adverse conditions; preserves DNA of the cell in a dormant state until conditions are favorable again
endoskeletal staining a differential staining technique that uses two stains to make bacterial endospores appear distinct from the rest of the cell
endosymbiotic theory the theory that mitochondria and chloroplasts arose as a result of prokaryotic cells establishing a symbiotic relationship within a eukaryotic host
endothelium layer of epithelial cells lining blood vessels, lymphatics, the blood-brain barrier, and some other tissues
endotoxin lipid A component of lipopolysaccharides in the outer membrane of gram-negative bacteria
enriched media media that contain additional essential nutrients to support growth
enrichment culture media providing growth conditions that favor the expansion of an organism present in low numbers
enteric bacteria of the family Enterobacteriaceae, which live in the human intestine
Enteritis inflammation of the lining of the intestine
enterobiosis intestinal infection caused by the pinworm Enterobius vermicularis
Enteroheamorrhagic E. coli (EHEC) E. coli bacteria that cause severe gastrointestinal illness with potential serious complications such as hemolytic uremic syndrome
enteroinvasive E. coli (EIEC) E. coli bacteria that cause relatively mild gastrointestinal illness
enteropathogenic E. coli (EPEC) E. coli bacteria that cause serious gastrointestinal illness
enterotoxigenic E. coli (ETEC) E. coli bacteria that cause a relatively mild illness commonly called traveler’s diarrhea
enterotoxin toxin that affects the intestines
Entero-Doudoroff (ED) pathway alternative glycolytic pathway used by some bacteria
enveloped virus a virus formed with a nucleic-acid packed capsid surrounded by a lipid layer
enzyme catalyst for biochemical reactions inside cells
enzyme immunoassay (EIA) type of assay wherein an enzyme is coupled to an antibody; addition of a chromogenic substrate for the antibody allows quantification or identification of the antigen bound by the antibody
enzyme-linked immunosorbent assay (ELISA) specialized form of EIA in which either the primary antibody or the antigen is first attached to a solid surface such as the well of a microtiter plate
epidermis the outermost layer of human skin
epididymitis coiled tube that transports sperm from the testes and passes it on to the vas deferens
epididymitis inflammation of the epididymis caused by a bacterial infection
epigenetic regulation chemical modification of DNA or associated histones to influence transcription
epigelosis flag of cartilage that covers the larynx during swallowing; diverts food to the esophagus and prevents it from entering the respiratory tract
epigelosis inflammation of the epigelosis
epiphyte a plant that grows on another plant
epitope smaller exposed region on an antigen that is recognized by B-cell and T-cell receptors and antibodies
Escherichia coli (E. coli) a class of Proteobacteria that are microaerophilic
equivalence zone region where the antibody–antigen ratio produces the greatest amount of precipitin in a precipitation reaction
erysipelas a skin infection, typically caused by Streptococcus pyogenes, that presents as a red, large, intensely painful, and sometimes ulcerated patch on skin involving the dermis, usually with clear borders, typically on the legs or face
erythema nodosum a condition that causes inflammation in the subcutaneous fat cells of the hypodermis resulting in red nodules
erythema redness at the site of inflammation, usually due to dilation of blood vessels in the area to help bring in white blood cells
erythrocyte red blood cell
erythrogenic toxin exotoxin produced by some strains of Streptococcus pyogenes; activity of the toxin can produce the characteristic rash of scarlet fever
erythromycin protein synthesis inhibitor of the macrolide class that is often used as an alternative to erythromycin
extracellular matrix material composed of proteoglycans and fibrous proteins secreted by some eukaryotic cells (e.g., cell wall cells); helps multicellular structures withstand physical stresses and coordinates signaling from the external surface of the cell to the interior of the cell
extracellular polymeric substances (EPS) hydrated gel secreted by bacteria in a biofilm containing polysaccharides, proteins, nucleic acids, and some lipids
extrachromosomal DNA additional molecules of DNA distinct from the chromosomes that are also part of the cell's genome
extravasation process by which leukocytes pass through capillary walls to reach infected tissue; also called diapedesis
F- (recipient) cell E. coli cell lacking the F plasmid and thus incapable of forming a conjugation pilus but capable of receiving the F plasmid during conjugation
F pilus (F pili) specialized type of pili that aids in DNA transfer between cells; conjugation pilus of E. coli
F plasmid (fertility factor) bacterial plasmid in E. coli containing genes able to conjugate, including genes encoding the formation of the conjugation pilus
F's (donor) cell E. coli cell containing the F plasmid, capable of forming a conjugation pilus
Fab region arm of an antibody molecule that includes an antigen-binding site
facultative anaerobe organism that grows better in the presence of oxygen but can proliferate in its absence
false negative result to a test for an infection or condition (e.g., presence of antigen, antibody, or nucleic acid) when the infection or condition is actually present
false positive result to a test for an infection or condition (e.g., presence of antigen, antibody, or nucleic acid) when the infection or condition is actually absent
fastidious organism organism that has extensive growth requirements
fatty acid lipid that contains long-chain hydrocarbons terminated with a carboxylic acid functional group
fatty acid methyl ester (FAME) analysis technique in which the microbe’s fatty acids are extracted, converted to volatile methyl esters, and analyzed by gas chromatography, yielding chromatograms that may be compared to reference data for identification purposes
Fc region region on the trunk of an antibody molecule involved in complement activation and opsonization
feedback inhibition mechanism of regulating metabolic pathways whereby the product of a metabolic pathway noncompetitively binds to an enzyme early on in the pathway, temporarily preventing the synthesis of the product
fermentation process that uses an organic molecule as a final electron acceptor to regenerate NAD+ from NADH such that glycolysis can continue
fibrinogen filamentous appendages found by the hundreds on some eukaryotic cells; composed of microfilaments in a 9+2 arrangement; used for locomotion
flavin adenine dinucleotide (FAD/FADH2) oxidized/reduced forms of a functional group in cells
floculent visible aggregation that forms between a substance in suspension (e.g., lipid in water) and antibodies against the substance
flow cytometry technique analyzing cells for fluorescence intensity; specific subsets of cells are usually labeled in some way prior to the analysis
fluconazole antifungal drug of the imidazole class that is administered orally or intravenously for the treatment of several types of systemic yeast infections
fluid mosaic model refers to the ability of membrane components to move fluidly within the plane of the membrane, as well as the mosaic-like composition of the components
flakes any of the parasitic nonsegmented flatworms (trematodes) that have an oral sucker and sometimes a second ventral sucker; they attach to the inner walls of intestines, lungs, large blood vessels, or the liver in humans
fluorescence microscope a microscope that uses natural fluorochromes or fluorescent stains to increase contrast
fluorescence-activated cell sorter (FACS) technique for using a flow cytometer to physically separate cells into two populations based on fluorescence intensity
fluorescent antibody (FA) techniques suite of assays that use a fluorescently labeled antibody to bind to and so make an antigen easy to visualize
fluorescent enzyme immunoassay (FEIA) EIA in which the substrate is a fluorogen that becomes fluorescent following reaction with the enzyme
fluorescent the ability of certain materials to absorb energy and then immediately release that energy in the form of light
fluorochromes fluorochromes that fluoresce (absorb and then emit light)
fluoruron nonfluorescent molecule that becomes fluorescent on enzyme or laser activation
fluorphore molecule that fluoresces when excited by light
fluoroquinolones class of synthetic antimicrobials that inhibit the activity of DNA gyrase, preventing DNA replication
focal infection infection in which the pathogen causes infection in one location that then spreads to a secondary location
focal length the distance from the lens to the image point when the object is at a definite distance from the lens (this is also the distance to the focal point)
focal point a property of the lens; the image point when light entering the lens is parallel (i.e., the object is an infinite distance from the lens)
folliculitis a skin infection characterized by localized inflammation of hair follicles, typically producing an itchy red rash
fonte inanimate item that may harbor microbes and aid in disease transmission
foodborne disease disease that is transmitted through contaminated food
fragmentation newly formed cells split away from the parent filament in actinomyces and cyanobacteria
frameshift mutation mutation resulting from either a deletion or a deletion in a number of nucleotides that, if not a multiple of three, changes every amino acid after the mutation
free ribosome eukaryotic ribosome found in the cytoplasm; synthesizes water-soluble proteins
Giardiasis intestinal infection caused by *Giardia lamblia*

Giants foot in the stomach or intestine

Gene expression production of proteins from the information contained in DNA through the processes of transcription and translation

Gene the cells that differentiate and reproduce by cell division

Gene therapy a form of treatment for diseases that result from genetic mutations; involves the introduction of nonmutated, functional genes into the genome of the patient, often by way of a viral vector

Generalized transudation transfer of a random piece of bacterial chromosome DNA by the phage

Generation time doubling time

Genetic code correspondence between mRNA nucleotide codons and the translated amino acids

Genetic engineering the direct alteration of an organism’s genes to achieve desirable traits

Genital herpes an STI caused by the herpes simplex virus

Genital warts soft, pink, irregular growths that develop in the external genitalia or anus as a result of human papillomavirus infection

Genome entire genetic content of a cell

Genomic library a repository of an organism’s entire genome maintained as cloned fragments in the genomes of strains of a host organism

Genomics the study and comparison of entire genomes, including the complete set of genes, their nucleotide sequence and organization, and their interactions with a species and with other species

Genotype full collection of genes that a cell contains within its genome

Germ theory of disease the theory that many diseases are the result of microbial infection

Gammaproteobacteria class of Proteobacteria that is very diverse and includes a number of human pathogens

Gastroenteritis inflammation of the lining of the stomach and intestine

Gametes reproductive cells which are produced in the gonads and are involved in sexual reproduction

Gamete a reproductive cell

Gametic phase of sexual reproduction

Gametogenesis the process of gamete production

Gamete the reproductive cell

Gammaglobulin a protein produced by plasma cells

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hyperthermophile a microorganism that has an optimum growth temperature close to the temperature of boiling water
hypertonic medium an environment in which the solute concentration outside a cell exceeds that inside the cell, causing water molecules to move out of the cell, resulting in crenation (shriveling) or plasmolysis.
hypophase tubular, filamentous structures that makes up most fungi
hypodermis the layer of tissue under the dermis, consisting primarily of fibroin and adipose connective tissue
hypotonic medium an environment in which the solute concentration inside a cell exceeds that outside the cell, causing water molecules to move into the cell, possibly leading to swelling and possibly lysis
iatrogenic disease caused by or acquired during a medical procedure
icosahedral three-dimensional, 20-sided structure with 12 vertices
IgA antibody dimer primarily found in breast milk, mucus, saliva, and tears
IgD membrane-body antibody monomer functioning as receptor on the surface of B cells
IgE antibody monomer involved in defense against parasites and allergic reactions
IgG antibody monomer most abundant in serum; able to cross placenta; most versatile class of antibody in terms of function
IgM antibody that is a monomer functioning as a receptor on surface of B cells but a pentamer when secreted in response to specific pathogens; first antibody to respond during primary and secondary responses
illuminator the light source on a microscope
image point (focus) a property of the lens and the distance of the object to the lens; the point at which an image is in focus (the image point is often called the focus)
imidazoles class of antifungal drugs that inhibit ergosterol biosynthesis
immune complex large group of antigens bound by antibodies; large enough to settle out of fluid suspension
immunochromatographic assay assay in which fluids are pulled through test strips by capillary action and protein molecules or antibodies are captured as they pass through the test strip
immuno fluorescence microscope and antibody-specific fluorochromes to determine the presence of specific pathogens in a specimen
immunofluorescence a technique in which antibody or antigen is localized in the colored bead, allowing visualization
immunogenicity the joining of two complementary single-stranded DNA molecules
immunodeficiency virus (HSV) retrovirus responsible for acquired immune deficiency syndrome (AIDS) in humans
immunohistochemistry (ICC) staining technique in which antibodies are detected as a signal using visualizing antibodies
immunolocalization the joining of two complementary single-stranded DNA molecules
immunoassay an assay in which antibodies are detected as a signal using a visualizing antibody
immunofluorescence a technique in which antibodies are captured as they pass through the test strip
immunostaining technique in which antibodies are detected as a signal using a visualizing antibody
immunosuppression a reduction in the functional activity of the immune system
impetigo a skin infection that may result in vesicles, blisters, or bullae especially around the mouth, commonly caused by Staphylococcus aureus and S. pyogenes, or a combination of both S. aureus and S. pyogenes
indirect antiglobulin test (IAT) see indirect Coombs’ test
indirect contact transmission transfer of an infectious agent between hosts through contact with a fomite
indirect Coombs’ test assay, performed in vitro prior to blood transfusions, that looks for antibodies against red blood cell antigens (other than the A and B antigens) that are unbound in a patient’s serum
indirect ELISA EIA in which an antigen from a pathogen is first attached to the wells of a microtiter plate; the antigen then captures antibodies from patient serum to determine whether the patient currently has or previously had the disease
indirect fluorescent antibody test assay for antigen-specific antibodies wherein the antigen captures the antibody, which is subsequently detected using a labeled anti-immunoglobulin mAb
induced mutation mutation caused by a mutagen
inducer small molecule that either activates or represses transcription
inducible operon bacterial operon, typically containing genes encoding enzymes in a degradative pathway, whose expression is induced by the substrate to be degraded and whose product is available for the cell to use, but that is otherwise repressed in the absence of the substrate
induction prophase DNA is excised from the bacterial genome
infection the successful colonization of a microorganism within a host
infectious arthritis (septic arthritis) inflammation of joint tissues in response to a microbial infection
infectious disease disease caused by a pathogen
infectious mononucleosis common and mild illness caused by Epstein-Barr virus (HHV-4) or cytomegalovirus (HHV-5); transmitted by direct contact with body fluids such as saliva
inflammation innate nonspecific immune response characterized by erythema, edema, heat, pain, and altered function, typically at the site of injury or infection but sometimes becoming systemic
influenza highly contagious and acute viral disease of the respiratory tract caused by the influenza virus
initiation factors proteins that participate in ribosome assembly during initiation
initiation of DNA replication stage of replication during which various proteins bind to the origin of replication to begin the replication process
initiation of transcription stage of transcription during which RNA polymerase binds to a promoter and transcription begins
initiation of translation stage of translation during which an initiation complex composed of the small ribosomal subunit, the mRNA template, initiation factors, GTP, and a special initiator tRNA forms, and the large ribosomal subunit then binds to the initiation complex
inoculum small number of cells added to medium to start a culture
inorganic phosphate (P)
insertion type of mutation involving the addition of one or more bases into a DNA sequence
integrate inhibitors antiviral drugs that block the activity of the HIV integrase responsible for recombination of a DNA copy of the viral genome into the host cell chromosome
intercalating agent molecule that slides between the stacked nitrogenous bases of the DNA double helix, potentially resulting in a frayed or shredded form
interference distortion of a light wave due to interaction with another wave
interferons cytokines released by cells that have been infected with a virus; stimulate antiviral responses in nearby cells as well as the cells secreting the interferons
interleukins cytokines largely produced by immune system cells that help coordinate efforts against invading pathogens
intermediate filaments one of a diverse group of cytoskeletal filaments that act as cables within the cell and anchor the nucleus, comprise the nuclear lamina, or contribute to the formation of desmosomes
intermediate host a host in which a parasite goes through one or more stages of its life cycle before migrating to the definitive host
intermittent common source spread a mode of disease transmission in which every infection originates from the same source and that source produces infections for a period before stopping and then starting again
intertrigo a rash that occurs in a skin fold
intestinal flu a trematode worm that infects the intestine, often caused by Fasciolopsis buski
intracellular targeting toxin see A-B toxin
intrinsic growth rate genetically determined generation time under specific conditions for a bacterial strain
invivo imaging sequence of a eukaryotic gene that does not code for protein and whose corresponding RNA sequences are removed from the primary transcript during splicing
intubation placement of a tube into the trachea, generally to open the airway or to administer drugs or oxygen
in-use test a technique for monitoring the correct use of disinfectants in a clinical setting; involves placing used, diluted disinfectant onto an agar plate to see if microbial colonies will grow
invasion dissemination of a pathogen through local tissues or throughout the body
iodophor compound in which iodine is complexed to an organic molecule, increasing the stability and efficacy of iodine as a disinfectant
ionizing radiation high-energy form of radiation that is able to penetrate surfaces and sterilize materials by damaging microbial cell components and DNA
ischemia condition marked by the inadequate flow of blood to the tissues
isograft transplant of tissues or organs from one member of the same species to another
isolevuglucosidin IgM class antibodies produced against A or B red blood cell antigens
isomers molecules that have the same atomic makeup but differ in the structural arrangement of the atoms
isomiazid antituberculosis drug that inhibits biosynthesis of mycolic acid; used for the treatment of mycobacterial infections
isopenoid branched lipid derived from five-carbon isoprene molecules
isotonic medium a solution in which the solute concentrations inside and outside the cell are approximately equal, thereby creating no net movement of water molecules across the cell membrane
ivermectin antihelminthic drug of the avermectin class that binds to invertebrate glutamate-gated chloride channels to block neuronal transmission in helminths
Japanese encephalitis arboviral disease caused by the Japanese encephalitis virus (JEV) and endemic to Asia
jaundice yellowish color of the skin and mucus membranes caused by bilirubin caused by a failure of the liver to effectively process the breakdown of hemoglobin
keratin a fibrous protein found in hair, nails, and skin
keratitis inflammation of the cornea
keratoconjunctionivitis inflammation of both the cornea and the conjunctiva
kidney organ that filters the blood, producing urine
kinase technique a method of acid-fast staining that does not use heat to infuse the primary stain, carbolfuchsin, into acid-fast cells
Kirk-Bauer disk diffusion test simple, rapid method for determining susceptibility and resistance of a bacterial pathogen to antibacterial drugs. The test involves drug-impregnated discs placed on an agar plate inoculated with a bacterial lawn.
Köhle’s spots white spots that form on the inner lining of the cheek of patients with measles
Kreb’s cycle cyclic pathway during which each two-carbon unit entering the cycle is further oxidized, producing three NADH, one FADH2, and one ATP by substrate-level phosphorylation, releasing two CO2 molecules and regenerating the molecule used in the first step; also called the citric acid cycle or the tricarboxylic acid cycle
kurv rare form of transmissible spongiform encephalopathy endemic to Papua New Guinea
lacrical duct connects the lacrimal gland to the lacrimal sac
lacrical gland a gland situated above the eye that secretes tears
lacrical punctum opening in each upper and lower eyelid
lacrical sac a to a reservoir for tears; also known as the dacrocyt or tear sac
lag period the time between antigen exposure and production of antibodies
lag phase interval before exponential growth of a microbial population during which cells adjust to a new environment
lauing strand strand of DNA made discontinuously by DNA polymerase
laryngitis inflammation of the larynx
larynxopharynx lower portion of the pharynx that connects to the larynx region of the respiratory tract containing the vocal cords; also referred to as the voice box
latent disease disease that goes into a dormant nonreplicative state after the acute disease and can persist in this state for years, with the risk of reactivation back into acute disease
latent virus virus that remains dormant in the host genome
lateral flow test see immunochromatographic assays
leading strand strand of DNA made continuously in the 5′ to 3′ direction by DNA polymerase
Legionnaires disease atypical pneumonia occurring in older individuals; caused by the inhalation of Legionella pneumophila aerosolized in water
leishmaniasis protozoan infection caused by Leishmania spp. and transmitted by sand flies
leporey see Hansen’s disease
leptospirosis bacterial infection of the kidney caused by Leptospira spp.; may spread to the liver, lungs, brain, and other organs
leukocidin class of exotoxin that targets and lyses leukocytes
leukocytes white blood cells of various types, including granulocytes, lymphocytes, and monocytes
leukotrienes lipid-based chemical mediators produced by leukocytes and other tissue cells; promote inflammation and allergic responses
lichen symbiotic association of a fungus with an alga or cyanobacterium
ligation repair of the sugar-phosphate backbone of the DNA, making the DNA molecule continuous
light chains the shorter identical peptide chains of an antibody molecule (two per antibody monomer), composed of variable and constant region segments
light-dependent reaction process by which energy from sunlight is absorbed by pigment molecules in photosynthetic membranes and converted into stored chemical energy in the forms of ATP and NADPH
light-harvesting complex group of multiple proteins and associated pigments that each may absorb light energy to become excited, and transfer this energy from one pigment molecule to another until the energy is delivered to a reaction center pigment
light-independent reaction process by which chemical energy, in the form of ATP and NADPH produced by the light-dependent reactions, is used to fix inorganic CO2 into organic sugar; usually referred to as the Calvin-Benson cycle
lincomycin naturally produced protein synthesis inhibitor of the lincomamide class that binds to the 50S subunit, inhibiting peptide bond formation
linosamides class of protein synthesis inhibitors that are similar to macrolides
linked recognition a mechanism whereby a B cell and the helper T cell with which it interacts recognize the same antigen
lipase extracellular enzyme that degrades triglycerides
lipid bilayer biological membranes composed of two layers of phospholipid molecules with the nonpolar tails associating to form a hydrophobic barrier between the polar heads; also called unit membrane
lipid macromolecule composed primarily of carbon and hydrogen; source of nutrients for organisms, a storage form for carbon and energy, a part of the structure of membranes, and may function as hormones, pharmaceuticals, fragrances, and pigments
lipopolysaccharide (LPS) lipid molecules with attached sugars that are found as components of gram-negative outer membranes
lipoprotein conjugated protein attached to a lipid
listeriais bacterial disease caused from the ingestion of the microbe Listeria monocytogenes
lithotroph chemotroph that uses inorganic chemicals as its electron source; also known as chemoaerotroph
live attenuated vaccine vaccine with live pathogen that has been attenuated to become less virulent, and can produce an active but subclinical infection
liver fluke a trematode worm that affects the bile duct of the liver, including Fasciola hepatica and F. gigantica
local infection infection in one limited area
log phase interval of growth when cells divide exponentially; also known as the exponential growth phase
leishmaniais a disease caused by the parasitic Lox lox worm, which is transmitted by deerflies; adult worms live in the subcutaneous tissue and cause inflammation, swelling, and eye pain as they migrate through the skin and the conjunctiva of the eye
lophotrichous having a single tuft of flagella located at one end of a bacterial cell
Appendix C

low G+C gram-positive bacteria that have less than 50% of guanine and cytosine nucleotides in their DNA
lumen space inside the cisternae of the endoplasmic reticulum in eukaryotic cells
Lyme disease tickborne disease caused by the spirochete Borrelia burgdorferi
lymph node bean-shaped organs situated throughout the body that contain areas called germinal centers, which are rich in B and T lymphocytes; also contain macrophages and dendritic cells for antigen presentation
lymphadenitis inflammation of the lymph nodes
lymphangitis inflammation of the lymphatic vessels
lymphogranuloma venereum infection caused by Chlamydia trachomatis in tropical regions
lyophilization rapid freezing, followed by placement under a vacuum, of a material so that water is lost by sublimation, thereby inhibiting microbial growth
lysis destruction of the host cell
lysozyme bacterium carrying the prophage
lysocellular change (phage conversion) alteration of host chromatin or phenotypes due to the presence of phage
lysocellular cycle life cycle of some phages in which the genome of the infecting phage is integrated into the bacterial chromosome and replicated during bacterial reproduction until it exices and enters a lytic phase of the life cycle
lysogyey process of integrating the phage into the host genome
lysosome an organelle of the endomembrane system that contains digestive enzymes that break down engulfed material such as foodstuffs, infectious particles, or damaged cellular components
lytic cycle infection process that leads to the lysis of host cells

M
M protein a streptococcal cell wall protein that protects the bacteria from being phagocytized. It is associated with virulence and stimulates a strong immune response
macrolides class of protein synthesis inhibitors containing a large, complex ring structure that binds to the 50s subunit, inhibiting peptide bond formation
macromolecule polymer assembled from of individual units, monomers, that bind together like building blocks
macronucleus larger nucleus in ciliate protozoa that have two nuclei; polyplid with a reduced genome of metabolic genes and derived from the micronucleus
macrophage element required in abundance in cells; account for approximately 95% of the cell’s dry weight
macrophages monocytes that have left the bloodstream and differentiated into tissue-specific phagocytes
mad cow disease form of transmissible spongiform encephalopathy primarily affecting cattle; can be transmitted to humans by consumption of contaminated cattle products
magnetotaxis movement of bacterial cells using a magnetic field to orient them
magnetotaxis directional movement of bacterial cells using flagella in response to a magnetic field
magnification the power of a microscope (or lens) to produce an image that appears larger than the actual specimen, expressed as a factor of the actual size
major histocompatibility complex (MHC) collection of genes that code for MHC glycoproteins expressed on the surface of all nucleated cells
malane a general feeling of being unwell
malaria potentially fatal, mosquito-borne protozoan infection caused by several species of Plasmodium and characterized by a relapping fever, nausea, vomiting, and fatigue

mas cell granulocytes similar in origin and function to basophils, but residing in tissues
matrix assisted laser desorption/ionization time of flight mass spectrometry (MALDI-TOF) technique in which the sample (e.g., a microbe colony) is mixed with a special matrix and irradiated with a high-energy laser to generate characteristic gaseous ions that are subjected to mass spectral analysis, yielding mass spectra that may be compared to reference data for identification purposes
maturation assembly of viral components to produce a functional virus
maternity 

measurable

naive T cell a T cell that has escaped the thymus after thymic selection but has not yet been activated
maximum growth pH highest pH value that an organism can tolerate for growth
maximum growth temperature highest temperature at which a microorganism will divide or survive
maximum permissible oxygen concentration highest concentration of oxygen at which an organism will grow
measles highly contagious respiratory disease caused by the measles virus (MeV); marked by an intense macular rash and high fever; also known as rubella
melioidosis antihelminthic drug of the benzimidazole class that binds to helminthic β-tubulin, preventing microtubule formation
mechanical transmission transfer of a pathogen between hosts by a mechanical vector
mechanical vector an animal that transfers a pathogen from one host to another or from a reservoir to a host without being infected by the pathogen itself
median infectious dose (ID₅₀) concentration of pathogen that will produce active infection in 50% of test animals inoculated
median lethal dose (LD₅₀) concentration of pathogen that kills 50% of infected test animals
medulla loosely packed layer of fungal filaments located underneath the cortex of a lichen
membrane attack complex (MAC) ring structure formed from complement proteins C5 through C9 that penetrating the membranes of a targeted cell, causing cell lysis and death
membrane filtration method to remove bacteria from liquid, typically heat-sensitive solutions, using filters with a effective pore size of 0.2 µm or smaller, depending on need
membrane filtration technique known volumes are vacuum filtered aseptically through a membrane with a pore size small enough to trap microorganisms, which are counted after growth on plates
membrane-bound ribosome BOS eukaryotic ribosome attached to rough endoplasmic reticulum
membrane-disrupting toxin toxin that affects cell membrane function by either forming pores or disrupting the phospholipid bilayer
memory B cell an activated and differentiated B cell that is programmed to respond to secondary exposure to a specific antigen
memory helper T cell a long-lived T cell programmed to recognize and quickly mount a secondary response to a specific pathogen upon re-exposure
memory the ability of the specific adaptive immune system to quickly respond to pathogens to which it has previously been exposed
ménage membranes that surround the brain
meningitis inflammation of the meningeal membranes that surround the brain
meningoencephalitis bacterial infection caused by Neisseria meningitidis that results in an inflammation of the meninges
meningoenphalitis inflammatory response that involves both the brain and the membranes that surround it
MERS Middle East respiratory syndrome; first described in Saudi Arabia in 2013; caused by a zoonotic coronavirus that results in flu-like symptoms
mesophile a microorganism that grows best at moderate temperatures, typically between about 20 °C and 45 °C
metabolism all of the chemical reactions inside of cells
metachromatic granule a type of inclusion containing a vibrant, polynuclear inorganic phosphate that appears red when stained with methylene blue
metagenomics the science of studying a collection of mRNA molecules produced from microbial communities; involves studying gene expression patterns from a collection of multiple species
metatranscriptomics the science of studying a collection of mRNA molecules produced from microbial communities; involves studying gene expression patterns from a collection of multiple species
methanogen microorganism that produces methane
metacholin-resistant Staphylococcus aureus (MRSA) pathogen resistant to all β-lactams through acquisition of a new low-affinity penicillin-binding protein, and often resistant to many other drug classes
metronidazole antibacterial and antiprotozoan drug of the nitroimidazole class that is activated in anaerobic target cell and introduces DNA strand breakage, thus interfering with DNA replication in target cells
MHC I molecule glycoprotein expressed on the surface of all nucleated cells and involved in the presentation of normal “self” peptides and foreign antigens from intracellular pathogens
MHC II molecule glycoprotein expressed only on the surface of antigen-presenting cells and involved in the presentation of foreign antigens from pathogens ingested by phagocytosis
micelle small spherical arrangement of amphipathic lipid molecules with nonpolar tails aggregated within the interior and polar heads forming the outer surface
microaerophile organism that requires oxygen at levels lower than atmospheric concentrations
microarray analysis a technique used to compare two samples of genomic DNA or cDNA; the DNA or cDNA fragments are immobilized on a chip and labeled with different fluorescent dyes, allowing for comparison of sequences or gene-expression patterns
microbe generally, an organism that is too small to be seen without a microscope; also known as a microorganism
microbial death curve graphical representation of the progress of a particular microbial control protocol
microbial ecology study of the interactions between microbial populations microbiology the study of microorganisms
microbiome all prokaryotic and eukaryotic microorganisms that are associated with a certain organism
microfilament cytoskeletal fiber composed of actin filaments
microinjection the direct injection of DNA into the cytoplasm of a eukaryotic cell using a glass micropipette
microcrinus smaller nucleus in ciliate protozoa that have two nuclei; diploid, somatic, and used for sexual reproduction through conjugation
micronutrient indispensable element present in cells in lower amounts than macronutrients; also called trace element
microorganism generally, an organism that is too small to be seen without a microscope; also known as a microorganism
microsporidium fungi that lack mitochondria, centrioles, and peroxisomes; some can be human pathogens
microtiter plates plastic dishes with multiple small wells
microtube hollow tube composed of tubing dimers (α and β tubulin); the structural component of the cytoskeleton, centrioles, flagella, and cilia
miliary tuberculosis hematogenous dissemination and spread of Mycobacterium tuberculosis from tubercules
minimal bacterial concentration (MBC) lowest antibacterial drug that kills ≥99.9% of a starting inoculum of bacteria
minimal inhibitory concentration (MIC) lowest concentration of an antibiotic drug that inhibits visible growth of a bacterial strain
minimum growth pH lowest pH value that an organism tolerate for growth
minimum growth temperature lowest temperature at which a microorganism will divide or survive
minimum permissible oxygen concentration lowest concentration of oxygen at which an organism will grow
misense mutation point mutation that results in a different amino acid being incorporated into the resulting polypeptide
mitochondrial matrix the innermost space of the mitochondrion enclosed by two membranes; the location of many metabolic enzymes as well as the mitochondrial DNA and 70S ribosomes
mitochondriun (plural: mitochondria) large, complex organelle that is the site of cellular respiration in eukaryotic cells
mode of action way in which a drug affects a microbe at the cellular level
moist-heat sterilization protocol that involves steaming under pressure in an autoclave, allowing the steam to reach temperatures higher than the boiling point of water
mold a multicellular fungus, typically made up of long filaments
molecular cloning the purposeful fragmentation of DNA followed by attachment to another piece of DNA to produce a recombinant molecule, followed by introduction of this recombinant molecule into an easily manipulated host to allow for the creation of multiple copies of a gene of interest
monoclonal antibodies (mAbs) antibodies produced in vitro that only bind to a single epitope
monoclonal having a single eye-piece
monocytes large, agranular, mononuclear leukocytes found in the peripheral blood; responsible for phagocytosis of pathogens and damaged cells
monocious refers to sexually reproducing organisms in which individuals have both male and female reproductive organs
monomer small organic molecule that binds with like molecules, forming a polymer or macromolecule
monosaccharide monomer for the synthesis of carbohydrate polymers; the simplest carbohydrate, called a simple sugar
monotrichous having one flagellum, typically located on one end of the bacterial cell
morbidity a state of illness
Morbidity and Mortality Weekly Report (MMWR) the trade/industry publication for epidemiologists, reporting US public health data compiled by the CDC
morbidity rate the number of cases of a disease expressed as a percentage of the population or number per standard part of the population, such as 100,000
mordant a chemical added to a specimen that sets a stain
mortality death
mortality rate the number of deaths from a disease expressed as a percentage of the population or number per standard part of the population, such as 100,000
most probable number (MPN) statistical value representing the viable bacterial population in a sample obtained after a series of dilutions and multiple tube inoculations
mRNA short-lived type of RNA that serves as the intermediary between DNA and the synthesis of protein products
mucociliary escalator system by which mucus and debris are propelled up and out of the respiratory tract by the beating of respiratory cilia and the mechanical actions of coughing or swallowing
mucoscience rare form of pneumonia that can be caused by an invasive infection of different fungi in the order Mucorales, such as Rhizopus or Mucor
mucous membrane moist layer of epithelial cells and interspersed goblet cells that lines the inner surfaces that carry or are bathed in antimicrobial secretions from the cells of the membrane
mucus viscous secretion produced by cells and glands in various mucous membranes throughout the body; helps trap and remove microbes and debris from the body
multidrug-resistant microbes (MDR) group of pathogens that carry one or more resistance mechanisms, making them resistant to multiple antimicrobials; also called superbugs
multidrug-resistant Mycobacterium tuberculosis (MDR-TB) strain of M. tuberculosis that are resistant to both rifampin and isoniazid, the drug combination typically prescribed for the treatment of tuberculosis
multiple sclerosis autoimmune attack on the myelin sheaths and nerve cells in the central nervous system
mumps a viral illness that causes swelling of the parotid glands; rare in the United States because of effective vaccination
murine typhus fleaborne infection caused by Rickettsia typhi and characterized by fever, rash, and pneumonia
mutation type of chemical agent or radiation that can induce mutations
mutant organism harboring a mutation that often has a recognizable change in phenotype compared to the wild type
mutation heritable change in the DNA sequence of an organism
mutualism type of symbiosis in which two populations benefit from, and depend on, each other
myasthenia gravis autoimmune disease affecting the acetylcholine receptors in the neuromuscular junction, resulting in weakened muscle contraction capability
mycelium vegetative network of branched, tubular hyphae
mycologic acids waxy molecules associated with peptidoglycan in some gram-positive, acid-fast bacteria, chiefly mycobacteria
mycology the study of fungi
Mycoplasma pneumoniae also known as walking pneumonia; a milder form of atypical pneumonia caused by Mycoplasmum pneumoniae
mycoses (mycosis, sing.) refers to diseases caused by fungi
mycoxin biologically active product of pathogenic fungi that causes adverse changes in the host cells
myelin sheath insulating layer that surrounds the axon of some neurons and helps to promote signal propagation
myocarditis inflammation of the heart muscle tissues
natural antibiotic antimicrobial compound that is produced naturally by microorganisms in nature
natural killer cells (NK cells) lymphoid cells that recognize and destroy abnormal target cells by inducing apoptosis
natural passive immunity transfer of maternal antibodies from mother to fetus (transplacentally) or infant via breastmilk
necrotizing fasciitis a serious infection, also known as flesh-eating disease, that leads to rapid destruction of tissue through the action of exotoxin A; it can be caused by S. pyogenes or other bacterial species
negative (-) single-strand RNA (-ssRNA) a viral RNA strand that cannot be translated until it is replicated into positive single-strand RNA by viral RNA-dependent RNA polymerase
negative stain a stain that produces color around the structure of interest while not coloring the structure itself
Nematoda phylum comprising roundworms
neonatal herpes herpes infection of the newborn, generally caused by infection during birth
neonatal meningitis meningitis caused by Group B streptococcus and primarily in neonates (less than 2 months old)
neonatal tetanus tetanus acquired through infection of the cut umbilical cord
neurocytosis parasitic invasion of brain tissues by the larva of the pork tapeworm, Taenia solium
neuromycosis any fungal infection of the nervous system
neurotransmitter compound that is released at the synapse of neurons to stimulate or suppress the actions of other cells
neutralism type of symbiosis that does not affect either of the two populations
neutralization binding of an antibody to a pathogen or toxin, preventing attachment to target cells
neutrophile organism that grows best at a near neutral pH of 6.5–7.5
neutrophils leukocytes with a multilobed nucleus found in large numbers in peripheral blood; able to leave the bloodstream to phagocytose pathogens in infected tissues; also called polymorphonuclear neutrophils (PMNs)
next generation sequencing a group of automated techniques used for rapid DNA sequencing
nicotine adenine dinucleotide (NAD+) oxidized/reduced forms of an electron carrier in cells
nicotine adenine dinucleotide phosphate (NADP+) oxidized/reduced forms of an electron carrier in cells
nitrogen fixation bacterial biochemical pathways that incorporate inorganic nitrogen gas into organic forms more easily used by other organisms
nitrogenuous base nitrogen-containing ring structure within a nucleotide that is responsible for complementary base pairing between nucleic acid sequences
nonenveloped virus virus particles that, unlike genes, do not encode proteins
nonenveloped virus virus particles that, unlike genes, do not encode proteins
nontoxic DNA regions of an organism’s genome that, unlike genes, do not encode proteins
noncommunicable disease disease that is not transmitted from one person to another
noncompetitive (allosteric) inhibitor molecule that binds to allosteric sites, inducing a conformational change in the enzyme’s structure that prevents it from functioning
noncritical item object that may contact intact skin but does not penetrate it; requires cleanliness but not a high level of disinfection
noncytic phosphorilation pathway used in photosynthetic organisms when both ATP and NADPH are required by the cell
nontoxic DNA regions of an organism’s genome that, unlike genes, do not encode proteins
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nongonococcal urethritis (NGU) a nonspecific infection of the urethra that is not caused by Neisseria gonorrhoeae
noninfectious disease disease caused by something other than an infectious agent (e.g., genetics, environment, nutritional deficiencies)
nonionizing radiation low-energy radiation, like ultraviolet light, that can induce dimer formation between two adjacent pyrimidine bases, resulting in DNA polymerase stalling and possible formation of a frameshift mutation
nonsense mutation point mutation that converts a codon encoding an amino acid (a sense codon) into a stop codon (a nonsense codon)
nontreponemal serologic tests qualitative and quantitative indirect diagnostic tests for syphilis
northern blot a technique in molecular genetics used to detect the amount of RNA made by a gene expression within a tissue or organism sample; RNA fragments within a sample are separated by agarose gel electrophoresis, visualized on a membrane, and then exposed to a specific DNA probe labeled with a radioactive or fluorescent molecular beacon to aid in detection
nosocomial disease disease acquired in a hospital setting
notifiable disease a disease for which all cases must legally be reported to regional, state, and/or federal public health agencies
nuclear envelope (also called the nuclear membrane) a structure defining the boundary of the nucleus; composed of two distinct lipid bilayers that are contiguous with each other and with the endoplasmic reticulum
nuclear lamina a meshwork of intermediate filaments (mainly lamins) found just inside the nuclear envelope; provides structural support to the nucleus
nucleic acid class of macromolecules composed of nucleotide monomers polymerized into strands
nucleoid concentrated area of DNA genome and associated proteins found in a prokaryotic cell that is not surrounded by a membrane
nucleoid-associated protein (NAP) protein that assists in the organization and packaging of the chromosome in prokaryotic cells
nucleolus a dense region within the nucleus where ribosomal RNA biosynthesis occurs and preribosomal complexes are made
nucleoside analog chemical that is structurally similar to a normal nucleotide base that can be incorporated into DNA instead of normal bases during replication but that has different base pairing rules than the normal base for which it was substituted, inducing mutation
nucleotide excision repair (dark repair) enzymatic mechanism to repair pyrimidine dimers by cutting the dimer-containing DNA strand on both sides of dimer, removing the intervening strand and replacing the bases with the correct ones
nucleotide nucleic acid monomer composed of a pentose sugar, a phosphate group, and a nitrogenous base
nucleus a membrane-bound structure of eukaryotic cells that houses the DNA genome
numerical aperture a measure of a lens’s ability to gather light
ocular lens on a microscope, the lens closest to the eye (also called an eyepiece)
oil immersion lens a special objective lens on a microscope designed to be used with immersion oil to improve resolution
Okazaki fragment short fragment of DNA made during lagging strand synthesis
oligopeptide peptide having up to approximately 20 amino acids
oligotroph organism capable of living in low-nutrient environments
opacity the property of absorbing or blocking light
operator DNA sequence located between the promoter region and the first coding gene to which a repressor protein can bind
operon a group of genes with related functions often found clustered together in the prokaryotic chromosome and transcribed under the control of a single promoter and operator repression sequence
ophthalmia neonatorum infection of the conjunctiva in newborns caused by Neisseria gonorrhoeae transmitted during childbirth
opportunistic pathogen microorganism that can cause disease in individuals with compromised host defenses
opsin any molecule that binds to and coats the outside of a pathogen, identifying it for destruction by phagocytes (examples include antibodies and the complement proteins C3b and C4b)
opsinization process of coating a pathogen with a chemical substance (an opsinon) that allows phagocytic cells to recognize, engulf, and destroy the pathogen more easily
optimum growth pH the pH at which an organism grows best
optimum growth temperature the temperature at which a microorganism’s growth rate is highest
optimum oxygen concentration the ideal concentration of oxygen for a particular microorganism
oral herpes an infection caused by herpes simplex virus that results in cold sores, most commonly on and around the lips
oral thrush Candida infection of the mouth
orchitis inflammation of one or both of the testes
organic molecule composed primarily of carbon; typically contains at least one carbon atom bound to one or more hydrogen atoms
organotroph chemotroph that uses organic molecules as its electron source; also known as chemoheterotroph
origin of replication specific nucleotide sequence where replication begins
opharynx area where air entering mouth enters the pharynx
osmotic diffusion of water across a semipermeable membrane
osmotic pressure the force or pressure generated by water diffusing across a semipermeable membrane, driven by differences in solute concentration across the membrane
osteomyelitis inflammation of bone tissue
osteoporosis a disease characterized by a low bone mass and microarchitectural deterioration of bone tissue
osteosarcoma a malignant bone tumor
osteosynthetic bone grafting procedure
otitis externa an infection of the external ear canal, most commonly caused by Staphylococcus aureus; often called swimmer’s ear
otitis inflammation of the ear
otitis media with effusion accumulation of fluid inside the middle ear with or without infection
Oucherley assay test in which antigen and antibody are added to neighboring wells in an agar gel, allowing visualization of precipitin arcs
outer membrane a phospholipid bilayer external to the peptidoglycan layer found in gram-negative cell walls
P
P (peptidyl) site functional site of an intact ribosome that binds charged tRNAs carrying amino acids that have formed peptide bonds with the growing polypeptide chain but have not yet dissociated from their corresponding tRNA
palatine tonsil lymphoid tissue located near the oropharynx
papilloma growth on the skin associated with infection by any of the human papilloma viruses (HPVs), commonly known as a wart
paracrine function refers to a cytokine signal released from a cell to a receptor on a nearby cell
parasitism type of symbiosis in which one population benefits while harming the other parasite the study of parasites
parenteral route means of entry by a pathogen through skin or mucous membranes when these barriers are breached
parasympathetic nervous system (PNS) the division of the autonomic nervous system that regulates involuntary functions
pathogen a disease-causing microorganism
pathogen-associated molecular patterns (PAMPs) common molecular motifs found on pathogens
pathogenicity ability of a microbial agent to cause disease
pattern recognition receptors (PRRs) receptors on the surface or in the interior of phagocytic cells that bind to pathogen-associated molecular patterns (PAMPs)
pellicle structure that underlies the plasma membrane in protists, providing additional support
pelvic inflammatory disease (PID) infection of the female reproductive organs that may spread from the vagina to the cervix, uterus, fallopian tubes, and ovaries
penetration entry of phage into a host cell through infection, endocytosis, or membrane fusion
penicillin β-lactam antibacterial that was the first cell wall synthesis inhibitor developed
penis external genital organ in males through which urine and semen are discharged
penicillin β-lactam antibacterial that appears to degrade KDNA in target cells, as well as inhibit protein synthesis
pentoxyphosphate pathway (PPP) alternative glycolytic pathway that produces intermediates used for the biosynthesis of nucleotides and amino acids; also called the phosphoglucomutase pathway or the hexose monophosphate shunt
peptic ulcer an ulcer in the lining of the stomach or duodenum, often associated with Helicobacter pylori
lysosome, leading to the destruction of the pathogens that results when the phagosome is fused with the compartment in a phagocytic cell which is pinched off from the membrane to form a particle are engulfed by membrane invagination, plasmid and also incorporated into a phage head monitors and fights infections lymphoid tissue in the ileum that under a microscope Petroff-Hausser counting chamber result from blood leaking out of damaged vessels petechiae the symptoms of whooping cough pertussis toxin known as whooping cough by a whooping sound during inhalation; commonly during which the patient returns to normal function persister free radical formation in cells; can be used as a peroxygen type of strong oxidizing agent that causes biosynthesis peroxisome peroxidase having numerous flagella covering the gastrointestinal tract that propel ingested material negative bacteria the space between the cell wall periplasmic space thymus responses in T cells that have already exited the periodontal disease most severe than gingivitis, spreading deeper into the tissues peripheral nervous system network of neurons that connects the CNS with organs, sensory organs, and muscles throughout the body peripheral tolerance mechanism by which regulatory T cells inhibit self-reactive immune responses in T cells that have already exited the thymus periplasmic space the space between the cell wall and the plasma membrane, primarily in gram-negative bacteria peristasis muscular contractions of the gastrointestinal tract that propel ingested material through the stomach, intestine, and, eventually, through the rectum and out of the body peritrichous having numerous flagella covering the entire surface of a bacterial cell peroxidase enzyme that catalyzes the detoxification of peroxides peroxisome in eukaryotic cells, a membrane-bound organelle (not part of the endomembrane system) that produces hydrogen peroxide to break down various types of molecules; also plays a role in lipid biosynthesis peroxynex strong oxidizing agent that causes from antigens in cells; can be used as a disinfectant or antiseptic persistor dormant cell that survives in the death phase and is resistant to most antibiotics pertussis vaccine that causes severe coughing fits followed by a whooping sound during inhalation; commonly known as whooping cough pertussis toxin main virulence factor accounting for the symptoms of whooping cough petechiae small red or purple spots on the skin that result from blood leaking out of damaged vessels Petroff-Hauser counting chamber calibrated slide that allows counting of bacteria in a specific volume under a microscope Peyer’s patches lymphoid tissue in the ileum that monitors and fights infections phagocytosis a phagocytic act of phagocytosis that is involved in the engulfment of a water molecule phagosome compartment in the cytoplasm of a phagocytic cell that contains the phagocytosed pathogens enclosed by the cell membrane phagosomes (autoagolysosomes) the evaluation of the effectiveness and safety of drugs on the basis of information from an individual’s genomic sequence as well as examination of changes in gene expression in response to the drug pharyngitis inflammation of the pharynx pharynx region connecting the nose and mouth to the larynx: the throat phase-contrast microscope a light microscope that uses an annular stop and annular plate to increase contrast phenol coefficient measure of the effectiveness of a chemical agent through comparison with that of phenol on Staphylococci aurous and Salmonella entericus serovar Typhi phenolics class of chemical disinfectants and antimicrobials characterized by a phenol group that denatures proteins and disrupts membranes phenotype observable characteristics of a cell or organism phosophodiester bonds linkage whereby the phosphate group attached to the 5’ carbon of the sugar of one nucleotide bonds to the hydroxyl group of the 3’ carbon of the sugar of the next nucleotide phosphogluconate pathway see pentose phosphate pathway phospholipase enzyme that degrades phospholipid phospholipid complex lipid that contains a phagosome group phospholipid-derivated fatty acids (PLFA) is a technique in which the membrane phospholipids are saponified to release the fatty acids of the phospholipids, which can be subjected to FAME analysis for identification purposes phosphorescence the ability of certain materials to absorb energy and then release that energy as light after a delay photosynthesis process whereby phototrophic organisms convert solar energy into chemical energy that can then be used to build carbohydrates photosynthetic pigment pigment molecule used by a cell to absorb solar energy; each one appears the color of light that it transmits or reflects photosystem organized unit of pigments found within a photosynthetic membrane, containing both a light-harvesting complex and a reaction center phototaxis directional movement using flagella in response to light phototropism organism that gets its energy from light phototrophic bacteria nonxontomorphous bacteria that use sunlight as their primary source of energy phylogeny the evolutionary history of a group of organisms phytoplancton photosynthetic plankton pia mater fragile and innermost membrane layer surrounding the brain pili long protein extensions on the surface of some bacterial cells; specialized F or sex pili aids in DNA transfer between cells pinocytosis a type of endocytosis in which small dissolved materials are endocytosed into smaller vesicles plague infectious epidemic disease caused by Fersina pestis plankton microscopic organisms that float in the water and are driven by currents; they may be autotrophic (phytoplankton) or heterotrophic (zooplankton) planktonic free-floating or drifting in suspension plantbodies monoclonal antibodies produced in plants that are genetically engineered to express mouse or human antibodies plaque clear area on bacterial lawn caused by viral lysis of host cells plasma cell activated and differentiated B cell that produces and secretes antibodies plasma fluid portion of the blood that contains all clotting factors plasma membrane (also called the cell membrane or cytoplasmic membrane) lipid bilayer with embedded proteins that defines the boundary of the cell plasmalemnaa protist plasma membrane plasmid small, circular, double-stranded DNA molecule that is typically independent from the bacterial chromosome plasmolysis the separation of the plasma membrane away from the cell wall when a cell is exposed to a hypertonic environment platelets cell fragments in the peripheral blood that originate from megakaryocyte cells in the bone marrow; also called thrombocytes Playthelmintes phylum comprising flatworms pleconaril an antiviral drug targeting picornaviruses that prevents the binding of virus particles upon their infection of host cells pleomorphic able to change shape pneumococcal meningitis bacterial infection caused by Streptococcus pneumoniae that results in an inflammation of the meninges Pneumocystis pneumonia common pulmonary infection in patients with AIDS; caused by P. jiroveci pneumonia pulmonary inflammation that causes the lungs to fill with fluids pneumonic plague rare form of plague that causes massive hemmorhages in the lungs and is communicable through aerosols point mutation mutation, most commonly a base substitution, that affects a single base pair point source spread a form of common source spread in which the transmission of a disease from the source occurs for a brief period that is less than the pathogen’s incubation period polar tube a tube-like structure produced by spores of Parastic Microsporidia fungi that pierces host cell membranes poliomyelitis (polio) disease caused by an infection of the enteric polio virus characterized by inflammation of the motor neurons of the brain stem and spinal cord; can result in paralysis poly-A tail string of approximately 200 adenine nucleotides added to the 3’ end of a eukaryotic primary mRNA transcript to stabilize it polycyclamidyl gel electrophoresis (PAGE) a method for separating populations of proteins and DNA fragments during Sanger sequencing of varying sizes by differential migration rates caused by a voltage gradient through a vertical gel matrix polycyclic mtrna single mtrna molecule commonly produced during precursur transcription that carries information encoding multiple polypeptides polyclonal antibodies antibodies produced in a normal immune response, in which multiple clones of B cells respond to many different epitopes on an antigen polynes class of antifungal drugs that bind to ergosterol to form membrane pores, disrupting fungal cell membrane integrity polyhedral virus virus with a three-dimensional shape with many facets polyhydroxybutyrate (PHB) a type of cellular inclusion surrounded by a polyhydroxilipid monolayer embedded with protein polymaker site or multiple cloning site (MCS) a short sequence containing multiple unique restriction enzyme recognition sites that are used for inserting foreign DNA into the plasmid after restriction digestion of both the foreign DNA and the plasmid polymer macromolecule composed of individual units, monomers, that bind together like building blocks. polymerase chain reaction (PCR) an in vitro molecular technique that rapidly amplifies the number of copies of specific DNA sequences to make the amplified DNA available for other analyses polymorphonuclear neutrophil (PMN) see neutrophils
polymyxins lipopolysaccharide antibiotics that target the lipopolysaccharide component of gram-
negative bacteria and ultimately disrupt the integrity of
their outer and inner membranes
polypeptide polymer having from approximately 20 to 50 amino acids
polyphagocytic refers to a grouping of organisms that
is not descended from a single common ancestor
polyribosome (polysome) structure including an
mRNA molecule that is being translated by multiple ribosomes concurrently
poly saccharide polymer composed of hundreds of monosaccharides linked together by glycosidic
bonds; also called glycogen
portal of entry anatomical feature of the body
through which pathogens can enter host tissue
portal of exit anatomical feature of the body through
which pathogens can leave diseased individual
positive (+) strand viral RNA strand that acts like
messenger RNA and can be directly translated inside
the host cell
positive stain a stain that colors the structure of
a stain that colors the structure of
port plate method a technique used for inoculating
plates with diluted bacterial samples for the purpose
of cell counting; cells are mixed with warm liquid
agar before being poured into Petri dishes
praziqantel antihelminthic drug that induces a
calcium influx into tapeworms, leading to spasm and
paralysis
precipitin complex lattice of antibody and antigen
that becomes too large to stay in solution
precipitin ring test assay in which layers of antiserum
and antigens in a test tube form precipitin at the
interface of the two solutions
prevalence the total number or proportion of
individuals in a population ill with a specific disease
primary amebic meningoencephalitis (PAM) acute and deadly parasitic infection of brain tissues
by the amoeba Naegleria fowleri
primary antibody in a sandwich ELISA, the
antibody that is attached to wells of a microtiter plate
to capture antigen from a solution, or in an indirect
ELISA, the antigen-specific antibody present in a
patient’s serum
primary cell culture cells taken directly from an
animal or plant and cultured in vitro
primary immunodeficiency genitic condition that
results in impaired immune function
primary infection initial infection produced by a
pathogen
primary lymphoid tissue one of two types of lymphatic tissue; comprises bone marrow and the thymus
primary pathogen microorganism that can cause disease in the host regardless of the effectiveness of
the host’s immune system
primary response the adaptive immune response
produced upon first exposure to a specific antigen
primary stain refers, in differential staining
techniques, to the first dye added to the specimen
primary structure bonding sequence of amino acids in a polypeptide chain protein macromolecule that
results when the number of amino acids linked
together becomes very large, or when multiple polypeptides are used as building subunits
primary transcript RNA molecule directly
synthesized by RNA polymerase in eukaryotes
before undergoing the additional processing required
to become a mature mRNA molecule
primase RNA polymerase enzyme that synthesizes the
RNA primer required to initiate DNA synthesis
primer short complementary sequence of five to 10
RNA nucleotides synthesized on the template strand
by primase that provides a free 3’-OH group to
which DNA polymerase can add DNA nucleotides
prion acellular infectious particle consisting of just
proteins that do cause progressive diseases in
animals and humans
prodromal period second stage of acute disease,
during which the pathogen continues to multiply in
the host and nonspecific signs and symptoms
come observable
progeny virus newly assembled virions ready for
release outside the cell
progeial body segment of a cestode (tapeworm)
prokaryote an organism whose cell structure does
not include a membrane-bound nucleus
prokaryotic cell a cell lacking a nucleus bound by a
complex nuclear membrane
promoter DNA sequence onto which the
transcription machinery binds to initiate transcription
propagated spread the progression of an infectious
disease from person to person, either indirectly or
directly, through a population of susceptible individuals as one infected individual transmits the
agent to others, who transmit it to others yet again
prophage phage genome that has incorporated into the
host genome
prospective study a research design that follows
cases from the beginning of the study through time
to associate measured variables with outcomes
prostate gland gland that contributes fluid to semen
prostate infection infectious disease of the prostate
gland that removes individual amino acids from the ends of
peptide chains
protease inhibitor class of antiviral drugs, used in
HV therapy and hepatitis C therapy, that inhibits viral-specific proteases, preventing viral maturation
protein signature an array of proteins expressed by
a cell or tissue under a specific condition
Proto bacteria phylum of gram-negative bacteria
proteomic analysis study of all accumulated proteins of an organism
proteomics the study of the entire complement of proteins in an organism; involves monitoring differences in gene expression patterns between cells at the protein level
protists informal name for diverse group of
eukaryotic organisms, including unicellular, colonial, and multicellular types that lack specialized tissues
proton motive force electrochemical gradient formed
by the accumulation of hydrogen ions (also known as protons) on one side of a membrane relative to the other protonoza (plural: protozoa) a unicellular eukaryotic organism, usually mobile
protozoans informal term for some protists,
generally those that are nonphotosynthetic,
unicellular, and motile protozoology the study of
prototzoa
provirus animal virus genome that has integrated into
the host chromosome
pseudohyphae short chains of yeast cells stuck
so close together
pseudomembrane grayish layer of dead cells, pus,
fibrin, red blood cells, and bacteria that forms on
mucous membranes of the nasal cavity, tonsils,
pharynx, and larynx of individuals with diphtheria
pseudomembranosus colitis inflammation of the
large intestine with the formation of a
desquamating pseudomembrane; caused by C. difficile
pseudopodia temporary projections involved in
amoeboid movement; these “false feet” form by gel-
sol cycling of actin polymerization/denpolymerization
psoriasis zoonotic Chlamydia infection from birds that causes a rare form of pneumonia
purple sulfur bacteria phototrophic bacteria that
oxidize hydrogen sulfide into elemental sulfur and
sulfuric acid; their purple color comes from pigments bacteriorhodopsins and carotenoids
purulent an infection that produces pus; suppurative
pus accumulation of dead pathogens, neutrophils,
tissue fluid, and other bystander cells that may have
been killed by phagocytes at the site of an infection
pyelonephritis an infection of one or both kidneys
pyocyanin blue pigments produced by some strains of
Pseudomonas aeruginosa
pyoderma any suppurative (pus-producing)
infection of the skin
pyoverdin a water-soluble, yellow-green or yellow-
brown pigment produced by some strains of
Pseudomonas aeruginosa
pyrimidines nitrogenous bases containing a single
six-carbon ring; includes cytosine and thymine in DNA
pyrophosphate (PPI) two connected phosphate
groups in solution
pyuria pus or white blood cells in the urine
real-time PCR (quantitative PCR, qPCR) a variant of PCR involving the use of fluorescence to allow for the monitoring of the increase in double-stranded template during a PCR reaction as it occurs, allowing for the quantitation of the original target sequence

receptor-mediated endocytosis a type of endocytosis in which extracellular ligands are targeted to specific cells through their binding to specific cell surface receptors

recombination A type of genetic engineering in which DNA from one organism is cut and inserted into DNA from another organism, resulting in a new combination of genetic material

recombinant DNA technology the process by which DNA from one organism is cut and new pieces of foreign DNA from a second organism are incorporated, statistically creating new combinations of genetic material within the organism

redox potential tendency for a molecule to acquire electrons and become reduced; electrons flow from molecules with lower to those with higher redox potentials to those with higher redox potentials

redox reaction Pairing of an oxidation reaction with a reduction reaction

reduction reaction chemical reaction that adds electrons to acceptor molecules, leaving them reduced

reemerging infectious disease A disease that was once under control or largely eradicated that has begun causing new outbreaks due to changes in susceptible populations, the environment, or the pathogen itself

reflection When light bounces back from a surface

reduction Bending of light waves, which occurs when a light wave passes from one medium to another

refractive index A measure of the magnitude of slowing of light waves by a particular medium

regulatory T cells T cells of T that are activated by self-antigens and serve to inhibit peripheral self-reacting T cells from causing damage and autoimmunity

rejection Process by which adaptive immune responses recognize transplanted tissue as non-self, mounting a response that destroys the tissue or leads to the death of the individual

relapsing fever Fever-like or tick-borne disease caused by Babesia microti or B. hermsi and characterized by a recurrent fever

replicating plating technique in which cells from colonies growing on a complete medium are inoculated onto various types of minimal media from colonies growing on a complete medium are inoculated onto various types of minimal media

relaxation of the nasolabial fold A technique in which the nasolabial fold is relaxed using a series of fine sutures, resulting in a smoother appearance of the mouth

ribonucleic acid (RNA) Single-stranded nucleic acid composed of ribonucleotides

ribonucleotides RNA nucleotides containing ribose as the pentose sugar component and a nitrogenous base

ribosome A complex intracellular structure that synthesizes proteins

riboswitch A region of noncoding RNA found within the 5' end of some prokaryotic mRNA molecules that may bind to a small intracellular molecule, influencing the completion of transcription and/or translation

ribulose bisphosphate carboxylase (RuBisCO) First enzyme of the Calvin cycle responsible for adding a CO₂ molecule onto a five-carbon ribulose bisphosphate (RuBP) molecule

resultor Large industrial autoclave used for moist heat sterilization on a large scale

retrospective study A research design that associates historical data with present cases

reverse transcriptase enzyme found in retroviruses that can make a copy of ssDNA from dsRNA

reverse transcriptase inhibitor A class of antiviral drugs that inhibit reverse transcription

reverse transcriptase PCR (RT-PCR) A variation of PCR used to amplify copies of a specific mRNA molecule that begins with the conversion of mRNA molecules to cDNA by the enzyme reverse transcriptase

Rye syndrome Potentially life-threatening sequela to some viral infections that result in the swelling of the liver and brain, as a result of vitamin A deficiency

Rh factor Blood group antigen on the surface of red blood cells

rhinitis Inflammation of the nasal cavity

rhodamine Structures made of rhodamine on some lichens; aid in attachment to a surface

ribonucleic acid (RNA) RNA produced during the process of transcription

ribosome A complex intracellular structure that synthesizes proteins

ribosomal RNA A type of RNA that is involved in the synthesis of proteins

riboswitches Structures of RNA that act as sensors for specific metabolites

RNA polymerase enzyme that adds nucleotides to the 3'-OH group of the growing mRNA molecule that are complementary to the template strand, forming covalent phosphodiester bonds between the nucleotides in the RNA

RNA polymerase enzyme that adds nucleotides to the 3'-OH group of the growing mRNA molecule that are complementary to the template strand, forming covalent phosphodiester bonds between the nucleotides in the RNA

RNA splicing process of removing intron-encoded RNA sequences from eukaryotic primary DNA transcripts and recoding those encoded by exons

RNA transcript mRNA produced during transcription

Rocky Mountain spotted fever Potentially fatal tick-borne disease caused by Rickettsia rickettsii characterized by fever, body aches, and a rash

rogue form Missed form of the PNP protein that is normally found in the cell membrane and has the tendency to aggregate in neurons, causing extensive cell death and brain damage

rolling circle replication Type of rapid unidirectional DNA synthesis of a circular DNA molecule

rosacea A skin condition affecting children, associated with human herpesvirus 6 (HHV-6)

rough endoplasmic reticulum A type of endoplasmic reticulum containing bound 80S ribosomes for the synthesis of proteins destined for the plasma membrane

route of administration method used to introduce a drug into the body

rRNA Type of stable RNA that is a major constituent of ribosomes, ensuring proper alignment of the mRNA and the ribosomes as well as catalyzing the formation of the peptide bond between two aligned amino acids during protein synthesis

rubella German measles, caused by the rubella virus

s. (running) purposeful, directional movement of a prokaryotic cell propelled by counterclockwise flagellar rotation

SARS Severe acute respiratory syndrome: caused by a zoonotic coronavirus that results in flu-like symptoms

SARS-CoV-2 Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

saturated fatty acid Lipid with hydrogen chains containing only single bonds, which results in the maximum number of hydrogen atoms per chain

scanning electron microscope (SEM) A type of electron microscope that bounces electrons off the specimen, forming an image of the surface

scanning probe microscope A microscope that uses a probe that travels across the surface of a specimen at a constant distance while the current, which is sensitive to the size of the gap, is measured

scanning tunneling microscope A microscope that uses a probe that is passed just above the specimen, detecting the electric current between the probe and the specimen
scarlet fever bacterial infection caused by Streptococcus pyogenes, marked by a high fever and a red, peeling skin rash
clostridial botulism food poisoning caused by Clostridium botulinum
appendicitis inflamed appendix
schistosomiasis helminthic infection caused by Schistosoma spp.; transmitted from a small intermediate host to human swimmers or bathers in freshwater
schizophrenia mental disorder characterized by a combination of symptoms including positive symptoms, negative symptoms, flat affect, thought disorganization, and disordered speech
sebaceous gland a gland located in hair follicles that secretes sebum
sebaceous cyst a solid structure that forms when sebaceous glands become blocked and filled with sebum
secondary antibody antibody to which an enzyme or reporter is attached for use in ELISA assays; in direct and sandwich ELISAs, it is specific for the antigen being detected; in indirect ELISA, it is specific for the primary antibody
secondary immunodeficiency impaired immune response due to infection, metabolic disturbance, poor diet, stress, or other acquired factors
secondary infection second infection that develops after a primary infection as a result of the primary disease compromising immune defenses or antibiotics, thus eliminating protective microbiota
secondary lymphoid tissue one of two types of lymphatic tissue: comprises the spleen, lymph nodes, Peyer’s patches, and mucosa associated lymphoid tissue (MALT)
secondary response the adaptive immune response produced in response to a specific antigen to which the body has previously been exposed
secretion extrusion of a molecule from a cell
secretory vesicle membranous sac that carries molecules through the plasma membrane to be released (secreted) from the cell
secretogogue a physiologic stimulus that induces the release of stored mediator from an endocrine or exocrine gland
selective toxicity desirable quality of an antimicrobial that minimizes killing or inhibits the growth of the target microbe while causing minimal or no harm to the host
selective media media that contain antibiotics that encourage the growth of some bacteria while inhibiting others
selfish DNA自私的DNA
selfish vector shuttle vector that carries genes for gene expression; it is complementary to the sense strand
selfish interest an interest in one’s own benefit at the expense of others
selfish replication process whereby each of the two parental daughter molecules replicates itself without regard for the survival of the other daughter molecule
selfish DNA replication pattern of DNA replication whereby each of the two parent DNA strands acts as a template for new DNA to be synthesized, producing hybrid old- and new-strand daughter molecules
self-critical item object that contacts mucous membranes but does not penetrate tissue; requires a high level of disinfection
seminal vesicles glands that contribute fluid to semen
semisynthetic antimicrobial chemically modified derivative of a natural antibiotic
sense strand strand of DNA that is transcribed for gene expression; it is complementary to the antisense strand
sepsis systemic inflammatory response to an infection that results in high fever and edema, causing organ damage and possibly leading to shock and death
septate hyphae hyphae that contain walls between individual cells; characteristic of some fungi
septic arthritis see infectious arthritis
septic shock serious condition marked by the loss of blood pressure resulting from an inflammatory response against a systemic infection
septicemia condition in which pathogens are multiplying in blood
septicemic plague form of plague that occurs when the bacterial pathogen gains access to the bloodstream
septum separating structure that forms during cell division; also describes the separating wall between cells in a filament
seroplasma (plural: seroplasmas) condition that arises as a consequence of infection
serial dilution sequential transfer of known volumes of culture samples from one tube to another to perform a series offold dilution of the original culture
seroconversion point in an infection at which antibody to a pathogen is detectable using an immunosassay
serotype strain or variation of the same species of bacteria; also called serovar
serovar specific strain of bacteria identified by agglutination using strain-specific antiserum
serum fluid portion of the blood after clotting has occurred; generally lacks clotting factors
serum sickness systemic type III hypersensitivity reaction
sesile attached to a surface
severe combined immunodeficiency disease (SCID) genetic disorder resulting in impaired function of B cells and T cells
sex pilus specialized type of pilus that aids in DNA transfer between some prokaryotic cells
sheath part of the tail on a bacteriophage that contracts to introduce the viral DNA into the bacterium
shigellosis gastrointestinal illness caused by Shigella bacteria, also called bacillary dysentery
shingles acute and painful rash that forms following the reactivation of a latent chickenpox infection
shock extreme drop in blood pressure that, among other causes, can result from a strong immune response to the activity of toxins or response to bacterial products and can result in death
shuttle vector a plasmid that can move between bacterial and eukaryotic cells
side chain the variable functional group, R, attached to the α carbon of an amino acid
sign objective and measurable indication of a disease
silent mutation point mutation that results in the same amino acid being incorporated into the resulting polypeptide
simple microscope a type of microscope with only one lens to focus the image of the specimen
simple staining a staining technique that uses a single dye
single-stranded binding protein protein that coats the single strands of DNA near each replication fork to prevent the single-stranded DNA from rewinding into a double helix
sinusitis inflammation of the sinuses
S-layer cell envelope layer composed of protein covering the cell walls of some bacteria and archaea; in some archaea, may function as the cell wall
slime layer a layer of gycocalyx with unorganized layers of polysaccharides that aid bacterial adherence to surfaces
smear a thin layer of a specimen on a slide
smooth endoplasmic reticulum smooth endoplasmic reticulum that lacks ribosomes, is involved in the biosynthesis of lipids and in carbohydrate metabolism, and serves as the site of detoxification of toxic compounds within the cell
soft chancre soft, painful ulcer associated with the STI chancroid
sonication method of microbial control that involves application of ultrasonic waves to form cavitation within a solution, including inside cells, disrupting cell components as a result
Southern blot a technique in molecular genetics used to detect the presence of certain DNA sequences within a given DNA sample; DNA fragments within the sample are separated by agarose gel electrophoresis, immobilized on a membrane, and then exposed to a specific DNA probe labeled with a radioactive or fluorescent molecular beacon to aid in detection
spliced transcript a transcript of a specific piece of bacterial chromosomal DNA near the site of integration by the plasmid
specificity the ability of the specific adaptive immune system to target specific pathogens or toxins
spike viral glycoprotein embedded within the viral capsid or envelope used for attachment to host cells
spirochete a group of long, thin, spiral-shaped fastidious bacteria that includes the human pathogens that cause syphilis, Lyme disease, and leptospirosis
spleen abdominal organ consisting of secondary lymphoid tissue that filters blood and captures pathogens and antigens that pass into it; also contains specialized macrophages and dendritic cells that are active for antigen presentation
splicing enzyme complex containing small nuclear ribonucleoproteins that catalyzes the splicing out of intron-encoded RNA sequences from the primary transcript during RNA maturation in eukaryotes
spontaneous generation the now-disproved theory that life can arise from nonliving matter
spontaneous mutation mutation not caused by a mutagen that occurs through DNA replication errors
sporadic disease an illness that occurs at relatively low levels with no discernible pattern or trend, frequently with no geographic focus
spores specialized cells that may be used for reproduction or may be specialized to withstand harsh conditions
sporotrichosis subcutaneous infection caused by the fungus Sporothrix schenckii, which causes skin lesions and can potentially spread to the lymphatic system; also known as rose gardener’s disease or rose thorn disease
sporulation the process by which a vegetative cell produces a dormant endospore
spread plate method a technique used for inoculating plates with diluted bacterial samples for the purpose of cell counting; the liquid sample is pipetted onto solid medium and spread uniformly across the plate
St. Louis encephalitis mosquito-borne viral infection of the brain that occurs primarily in the central and southern United States
stage the platform of a microscope on which slides are placed
staining the addition of stains or dyes to a microscopic specimen for the purpose of enhancing contrast
staphylococcal food poisoning gastrointestinal illness caused by toxins produced by Staphylococcus aureus
staphylolysins a class of staphylococcal exotoxins that are cytotoxic to skin cells and white blood cells
starch energy-storage polysaccharide in plants; composed of two types of glucose polymers: amylose and amyllopectin
start codon AUG codon, specifying methionine, which is typically the codon that initiates translation
stationary phase interval during which the number of cells formed by cell division is equal to the number of cells dying
stereosomers isomers that differ in the spatial arrangements of atoms
sterilant strong chemical that effectively kills all microbes and viruses in or on an inanimate item
sterile field specific area that is free of all vegetative microbes, endospores, and viruses
sterilization protocol that completely removes all vegetative cells, endospores, and viruses from an item
steroid lipid with complexed, ringed structures found in cell membranes and hormones
sterol the most common type of steroid; contains an OH group at a specific position on one of the molecule’s carbon rings
**Antimicrobial use**

Sterilization and gases, allowing it to effectively penetrate the substance known as *Euglena*.

**Superior function**

Layer of dead, keratinized cells that forms the uppermost layer of the epidermis.

**Strep throat** (streptococcal pharyngitis)

Bacterial pharyngitis caused by *Streptococcus pyogenes*.

**Streptococcal toxic shock-like syndrome (STSS)**

Condition similar to *Staphylococcus* toxic shock syndrome but with greater likelihood of bacteremia, necrotizing fasciitis, and acute respiratory distress syndrome.

**Stroma**

A gel-like fluid that makes up much of a body organ's volume, and in which the thylakoids floats.

**Strongyloides stercoralis**

A parasitic nematode.

**Subclinical disease**

A disease process that does not present any signs or symptoms.

**Subcutaneous mycosis**

Any fungal infection that floats in the subcutaneous tissue or skin.

**Substrate-level phosphorylation**

The transfer of a phosphate group from ATP to a substrate to form a phosphorylated product.

**Subtype 17 cells**

Subtype of T cells that stimulate cytotoxic T cells, macrophages, neurotransmitters, and NK cells.

**Subtype T cells**

Subtype of T cells that stimulate B cells and direct their differentiation; also involved in directing antibody class switching.

**Subtype 2 cells**

Subtype of T cells that stimulate B cells and direct their differentiation; also involved in directing antibody class switching.

**Subtype 1 cells**

Subtype of T cells that stimulate cytotoxic T cells, macrophages, neurotransmitters, and NK cells.

**Sulfonamides**

Sulfur-containing compounds that inhibit bacterial enzyme systems.

**T cell**

A lymphocyte that serves as the central receptor of the immune system.

**Teratogenic**

A substance that is able to disrupt the normal development of an embryo or fetus.

**Tetanus**

A bacterial disease caused by exotoxin produced by *Clostridium tetani* that causes a rigid paralysis.

**Tetracyclines**

A class of protein synthesis inhibitors that bind to the 3O5 subunit, blocking the association of tRNAs with the ribosome during translation.

**T-helper cells**

Helper T cell that can activate a B cell without cooperation from an antigen-presenting cell.

**T-helper 2 cells**

Subtype of T cells that stimulate B cells and direct their differentiation; also involved in directing antibody class switching.

**Therapeutically**

Essential to the management of a disease.

**Thioglycolate medium**

Medium designed to test the aerotolerance of bacteria; it contains a low concentration of agar to allow motile bacteria to move throughout the medium.

**Thio-urease**

The enzyme that catalyzes the breakdown of thiourea in anaerobic conditions.

**Thymocyte**

Lymphocyte that serves as the central orchestrator, bridging humoral, cellular, and innate immunity, and serves as the effector cells of cellular immunity: T cell.

**Thymus**

A lymphoid organ located in the superior mediastinum, which is derived from the third pharyngeal pouch and consists of two bilobate lateral masses.

**Thymic cyst**

A congenital malformation of the thymus gland.

**Thymic stroma**

A gel-like fluid that makes up much of a body organ's volume, and in which the thylakoids floats.

**Thylakoid membranes**

Membranous sacs found in the stroma of chloroplasts; site of photosynthesis.

**Tinctorial**

Relating to the ability of a substance to confer color.

**Throat**

A passage through the pharynx that connects the mouth to the larynx and esophagus.

**Thrombocytopenia**

A decrease in the number of circulating platelets.

**Thrombosis**

The formation of a blood clot in a blood vessel.

**Thrombus**

A blood clot that forms in a blood vessel.

**Thymidine**

A component of DNA and RNA that is derived from deoxyribose and adenine.

**Thymidine dimer**

A covalent linkage between two thymine DNA nucleotides.

**Thymus**

A lymphoid organ located in the superior mediastinum, which is derived from the third pharyngeal pouch and consists of two bilobate lateral masses.

**Thyroid gland**

A small organ located at the base of the neck, just in front of the trachea, that produces hormones that regulate the body's metabolism.

**Thyroiditis**

Inflammation of the thyroid gland, which can be caused by a variety of conditions, including autoimmune disorders, infections, or trauma.

**Thyroglobulin**

A glycoprotein that is produced by follicular cells of the thyroid gland and serves as a storage form of thyroid hormones.

**Thyroid hormone**

Hormones produced by the thyroid gland that regulate metabolic rate, growth, and development.

**Thyroid stimulating hormone (TSH)**

A hormone produced by the pituitary gland that stimulates the thyroid gland to produce thyroid hormones.

**Thyroidectomy**

The surgical removal of all or part of the thyroid gland.

**Thymus**

A lymphoid organ located in the superior mediastinum, which is derived from the third pharyngeal pouch and consists of two bilobate lateral masses.

**Thymus cortex**

The outermost region of the thymus gland, which contains a high density of thymic medullary epithelial cells.

**Thymus medulla**

The innermost region of the thymus gland, which contains a low density of thymic medullary epithelial cells.

**Thymic stroma**

A gel-like fluid that makes up much of a body organ's volume, and in which the thylakoids floats.

**Thyroxine**

A hormone produced by the thyroid gland that regulates the body's metabolism.

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Appendix C

transient microbiota

the structure of supercoiled chromosomes,

foreign DNA from a different species has been

DNA replication

topoisomerase II enzyme responsible for facilitating
topological transitions of DNA, relaxing it from its

transient state

toxemia presence of toxins in the blood

toxic shock syndrome severe condition marked by

bacterial superantigens, toxic shock syndrome toxin

toxigenic ability of a pathogen to produce toxins
to cause damage to host cells

toxin produced by a pathogen

toxoid vaccine that contains inactivated bacterial toxins

toxoplasmosis typically asymptomatic protozoan infection caused by Toxoplasma gondii, and transmitted through contact with cysts in cat feces; infections in pregnant women may cause birth defects or m miscarriage

trace element indispensable element present in cells in lower amounts than macronutrients; also called micronutrient

treacha also known as the windpipe, this is a stiffened tube of cartilage that runs from the larynx to the bronchi

trachoma a type of conjunctivitis, caused by Chlamydia trachomatis, that is a major cause of preventable blindness

transcription bubble region of unwinding of the DNA double helix during transcription

transcription factors proteins encoded by regulatory genes that function by influencing the binding of RNA polymerase to the promoter and allowing its progression to transcribe structural genes

transcription process of synthesizing RNA using the information encoded in DNA

transcriptomics the study of the entire collection of mRNA molecules produced by cells; involves monitoring differences in gene expression patterns between cells at the mRNA level

transduction mechanism of horizontal gene transfer in bacteria in which genes are transferred through viral infection

transendothelial migration process by which circulating leukocytes exit the bloodstream via the microvascular endothelium

transfection the introduction of recombinant DNA molecules into eukaryotic hosts

transformation mechanism of horizontal gene transfer in bacteria in which naked environmental DNA is taken up by a bacterial cell

transgenic describing an organism into which foreign DNA from a different species has been introduced

transient microbe microorganisms, sometimes pathogenic, that are only temporarily found in the human body

two-photon microscope a microscope that uses long-wavelength or infrared light to fluoresce fluorochromes in a specimen

tympanic membrane also referred to as the eardrum, this structure separates the outer and middle ear

type I diabetes mellitus hyperglycemia caused by an autoimmune disease affecting insulin production by β cells of the pancreas

type I hypersensitivity rapid-onset allergic reaction due to cross-linking of antigen-antibody complexes on the outside of mast cells, resulting in release of inflammatory mediators

type II hypersensitivity cytotoxic reaction triggered by IgG and IgM antibodies binding to antigens on cell surfaces

type III hypersensitivity inflammatory reaction induced by formation of immune complexes and their deposition in tissues and blood vessels

type IV hypersensitivity delayed T-cell-mediated inflammatory reaction that takes longer to manifest than the first three hypersensitivity types, due to the need for activation of antigen-presenting cell and T-cell subsets

typoid fever serious illness caused by infection with certain serotypes of Salmonella

U

UHT pasteurization method of pasteurization that exposes milk to ultra-high temperatures (nearly 140 °C) for a few seconds, effectively sterilizing it so that it can be sealed and stored for long periods without refrigeration

ulcer open sore

ultramicrotome a device that cuts thin sections for electron microscopy

unit membrane biological membrane composed of two layers of phospholipid molecules with the nonpolar tails associating to form a hydrophobic barrier between the polar heads; also called lipid bilayer

unsaturated fatty acid lipid with hydrogen carbon chains containing one or more carbon-carbon double bonds and subsequently fewer than the maximum number of hydrogen atoms per chain

uracil pyrimidine nitrogenous base found only in RNA nucleotides

ureter duct that transports urine from the kidneys to the urinary bladder

urertheris inflammation of the ureter

urethra duct through which urine passes from the urinary bladder to leave the body through the urinary meatus

urethritis inflammation of the urethra

urinary bladder an organ that stores urine until it is ready to be excreted

urinary meatus the opening through which urine leaves the body

urine-dilution test a technique for determining the effectiveness of a chemical disinfectant on a surface; involves dipping a surface in a culture of the targeted microorganism, disinfecting the surface, and then transferring the surface to a fresh medium to see if bacteria will grow

vaccination inoculation of a patient with attenuated pathogens or antigens to activate adaptive immunity and protect against infection

vagina female reproductive organ that extends from the vulva to the cervix

vaginosis an infection of the vagina caused by overgrowth of resident bacteria

vancomycin cell wall synthesis inhibitor of the glycopeptide class
vancomycin-intermediate Staphylococcus aureus (VISA) pathogen with intermediate vancomycin resistance due to increased targets for and trapping of vancomycin in the outer cell wall

vancomycin-resistant enterococci (VRE) pathogens resistant to vancomycin through a target modification of peptidoglycan subunit peptides that inhibit binding by vancomycin

vancomycin-resistant Staphylococcus aureus (VRSA) pathogen with resistance to vancomycin that has arisen as a result of the horizontal gene transfer of vancomycin resistance genes from VRE

vaccination the historical practice of inoculating a healthy patient with infectious material from a person infected with smallpox in order to promote immunity to the disease

deviation pair two ducts in the male reproductive system that conduct sperm from the testes and seminal fluid to the ejaculatory duct

vasculitis inflammation affecting blood vessels (either arteries or veins)

VDRL (Venereal Disease Research Laboratory) test test for syphilis that detects anti-treponemal antibodies; results are expressed as either a positive or negative reaction with cardiolipin extracted from beef heart tissue

vector animal (typically an arthropod) that transmits a pathogen from one host to another host; DNA molecules that carry DNA fragments from one organism to another

vegetative cell a cell that is actively growing and dividing, and does not contain an endospore

vehicle transmission transfer of a pathogen between hosts via contaminated food, water, or air

vein blood vessel that returns blood from the tissues to the heart for recirculation

direct transmission transfer of a pathogen from mother to child during pregnancy, childbirth, or breastfeeding

gene transfer transfer of genes from parent to offspring

visible cell live cell; live cells are usually detected as colony-forming units

plate count direct method of measuring microbial growth in a culture; the number of viable or live cells is usually expressed in CFU/mL

conjugation process of genetic exchange between bacterial cells

envelope lipid membrane obtained from phospholipid membranes of the cell that surrounds the capsid

hemagglutination inhibition assay assay used to quantify the amount of neutralizing antibody against a virus by showing a decrease in hemagglutination caused by a standardized amount of virus

titer number of virions per unit volume

virulence characteristic that gives a pathogen the ability to cause infection and disease

virulent phage bacteriophage for which infection leads to the death of the host cell; a phage that undergoes the lytic cycle

virus an acellular microorganism, consisting of proteins and genetic material (DNA or RNA), that can replicate itself by infecting a host cell

virusoid small piece of RNA associated with larger RNA of some infectious plant viruses

volutin inclusion of polymerized inorganic phosphate; also called metachromatic granules

vulva the female external genitalia

W

water activity water content of foods or other materials

wavelength the distance between one peak of a wave and the next peak

Well's disease advanced stage of leptospirosis in which the kidney and liver become seriously infected

West African trypanosomiasis chronic form of African trypanosomiasis caused by Trypanosoma brucei gambiense

West Nile encephalitis mosquito-borne disease caused by the West Nile virus (WNV) that can result in swelling of the brain and death in severe cases

western blot technique used to detect the presence of a certain protein within a given protein sample in which proteins within the sample are separated by PAGE, immobilized on a membrane, and then exposed first to an antibody that binds to the protein of interest and then second to an antibody equipped with a molecular beacon that will bind to the first antibody

western equine encephalitis serious but rare mosquito-borne viral infection of the brain that is found primarily in the central and western United States

wet mount a slide preparation technique in which a specimen is placed on the slide in a drop of liquid

wheel-flare reaction localized type I hypersensitivity reaction, involving a raised, itchy bump (wheal) and redness (flare), to injected allergen

whooping cough common name for pertussis

wild type phenotype of an organism that is most commonly observed in nature

Winterbottom's sign acute swelling of lymph nodes at the back of the neck that is an early sign of African trypanosomiasis

wobble position third position of a codon that, when changed, typically results in the incorporation of the same amino acid because of the degeneracy of the genetic code

World Health Organization (WHO) international public health organization within the United Nations; monitors and communicates international public health information and coordinates international public health programs and emergency interventions

X

xenobiotic compound synthesized by humans and introduced to an environment in much higher concentrations than expected in nature

xenograft transplanted tissue from a donor that is of a different species than the recipient

X-linked agammaglobulinemia genetic disorder resulting in an inability to produce antibodies

x-y mechanical stage knobs knobs on a microscope that are used to adjust the position of the specimen on the stage surface, generally to center it directly above the light

Y

yeast any unicellular fungus

yeast infection fungal infection of the vagina typically caused by an overgrowth of resident Candida spp.

yellow fever mild to potentially fatal mosquito-borne viral disease caused by the yellow fever virus

Z

Ziehl-Neelsen technique a method of acid-fast staining that uses heat to fixate the primary stain, carbol fuchsin, into acid-fast cells

zone of inhibition clear zone around a filter disk impregnated with an antimicrobial drug, indicating growth inhibition due to the antimicrobial drug

zoonotic disease any disease that is transmitted to humans by animals

zooplankton heterotrophic plankton

Z-scheme electron flow seen in noncyclic photophosphorylation in plants, algae, and cyanobacteria due to the use of both PSI and PSII

zygospores spores used by Zygomycetes for sexual reproduction; they have hard walls formed from the fusion of reproductive cells from two individuals

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**Answer Key**

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