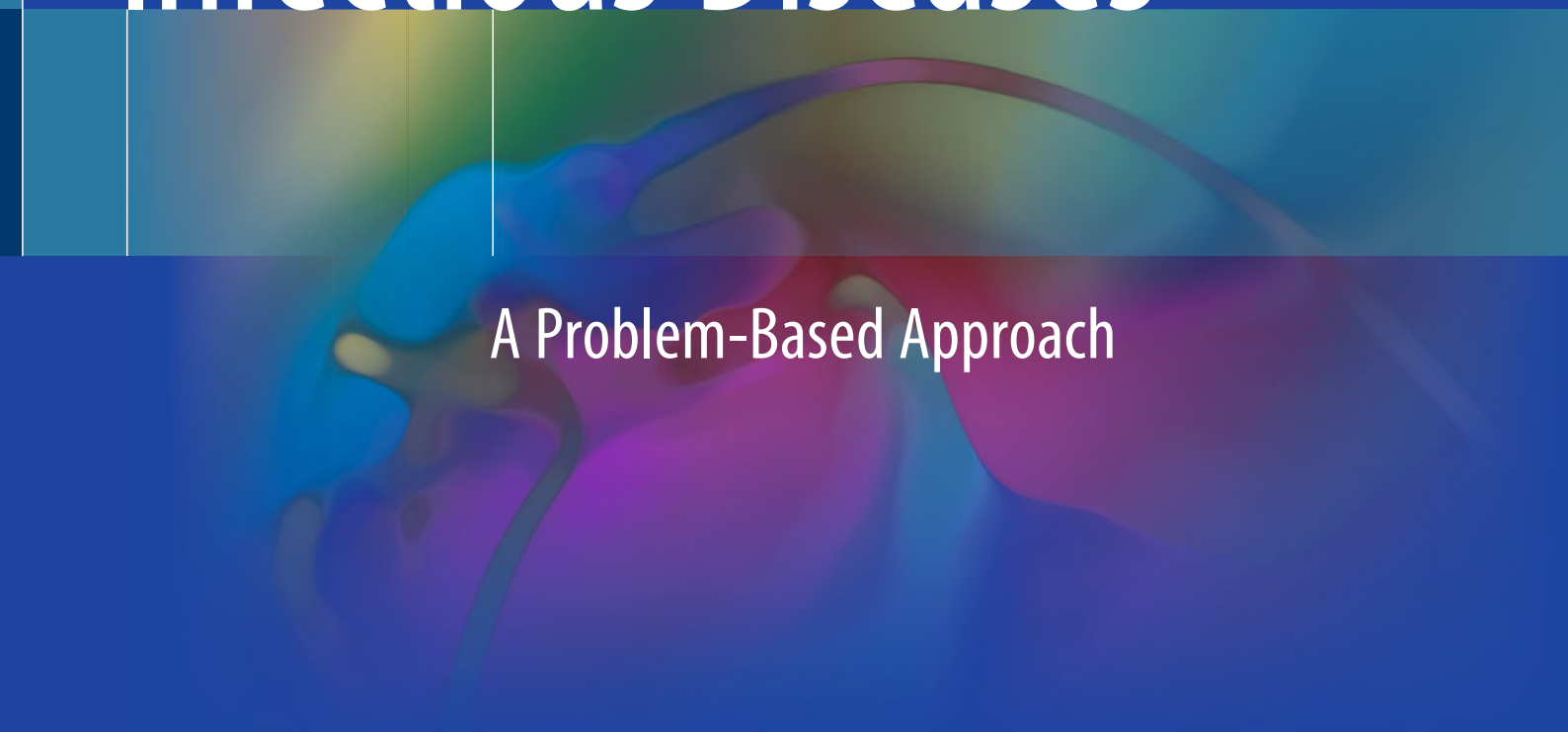
Joseph Domachowske
*Editor*

# Introduction to Clinical Infectious Diseases

## A Problem-Based Approach



Springer

# Introduction to Clinical Infectious Diseases

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A Problem-Based Approach

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I dedicate this book to the three people in my life who have taught me the most along the way:
Mary Beth
James
Elizabeth
Please keep up the good work. I love you dearly.

# Preface

» "Education is not filling a bucket, but lighting a fire" Plutarch circa 85AD

The most authoritative infectious disease medical textbooks, some in their 8th or 9th edition, can be found on the bookshelves of nearly every infectious disease physician currently in practice. They are written, updated and edited by world experts in the field and include thousands of pages of details on everything from amebic meningoencephalitis to zoonotic infections. The breadth and depth of the information they provide is invaluable to those who are practicing in the subspecialty, but their comprehensive format make them impractical for use during month-long clinical electives in infectious disease, or during rotations in outpatient primary care or hospital medicine. *Introduction to Clinical Infectious Diseases: A Problem-Based Approach* was developed to introduce student doctors, resident physicians, subspecialty fellows and other health provider trainees to the field of infectious diseases, by emphasizing basic concepts and building upon them. Infectious diseases impact all areas of clinical medicine, with the more severe or unusual problems typically requiring a multidisciplinary team management approach. The reader will appreciate that, while many of the chapters included in this book are written by infectious disease specialists in internal medicine, pediatrics or both, others are authored by pediatricians, specialists in adolescent medicine, surgical subspecialists, gastroenterologists, cardiologists, emergency medicine specialists, hospitalists, pharmacists and clinical microbiologists. I know each of the corresponding authors personally. Many of them taught me during medical school, residency and fellowship. Others were students, residents or fellows who once worked with me on our clinical infectious disease team, and are now enjoying their successful careers in academic medicine. All of them are gifted teachers with an innate talent to spark fires of curiosity in their trainees. I thank every one of them for their efforts and dedication in developing this book. "Introduction to Clinical Infectious Diseases: A Problem-Based Approach" is not meant to be comprehensive; it's meant to engage the learner, instruct on basic concepts, and provide a framework on the approach to common and classic infectious disease problems.

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# Infections of the Skin and Lymph Nodes

Contents

# Bacterial Infections of the Skin and Skin Structures

*Jennifer A. Nead*




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**Learning Objectives**

- Review the clinical presentation, microbiologic etiology, and management of common skin and skin structure infections including cellulitis and abscess.
- Highlight unusual and unique bacterial pathogens associated with infections following bite wounds and aquatic injuries/exposures.
- Recognize risk factors and clinical presentations that suggest less common pathogens and raise suspicion for underlying immunodeficiency.

## 1.1 Introduction to the Problem

Bacterial skin and skin structure infections (also referred to as skin and soft tissue infections) involve the skin layers and underlying connective tissue. Cellulitis and cutaneous abscess are frequent reasons for outpatient office visits and for hospital admissions. This chapter reviews the common bacterial pathogens involved in skin and skin structure infections as well as the unusual and unique pathogens associated with specific risk factors and exposures. A complete history and physical examination is critical to distinguish between different types of skin and skin structure infections. In addition, a detailed history regarding exposures and underlying risk factors assists in identifying circumstances where unique or uncommon pathogens need to be considered as possible etiologic agents. This approach guides providers to make the correct diagnosis, tailor a management plan directed to the suspected pathogen(s), and use antibiotics and other resources wisely.

## 1.2 Definitions

**Aquatic wound infection** – a skin and skin structure infection that develops after a freshwater- or saltwater-related injury or after a wound is exposed to an aquatic source

**Abscess** – a localized cavity of pus in the dermis or subcutaneous space with surrounding inflammation [1]

**Bite wound infection** – a skin and skin structure infection that develops after an animal or human bite

**Cellulitis** – a bacterial infection involving the dermis and subcutaneous tissue that typically spreads rapidly [2]

**Dermis** – the skin layer below the epidermis that is composed of elastic tissue, collagen, and reticular fibers [3]

**Epidermis** – outermost skin layer that is avascular and serves as a barrier between the host and the environment [3]

**I&D** – incision and drainage; a surgical procedure whereby an abscess is cut open to facilitate removal of the infected material

**Lymphangitis** – an infection of the lymphatic vessels; the erythematous streak that begins at the infection site and extends toward the local or regional draining lymph nodes seen on physical examination is the infected lymphatic vessel

**MSSA** – methicillin-resistant *Staphylococcus aureus*

**MRSA** – methicillin-sensitive *Staphylococcus aureus*

**Purulent cellulitis** – cellulitis with associated purulent drainage; a drainable abscess is not present [2]

**SIRS** – *S*ystemic *I*nflammatory *R*esponse *S*yndrome manifested by fever or hypothermia, tachypnea, tachycardia, and leukocytosis or leukopenia [4]

**Subcutaneous tissue** – anatomical area underneath the dermis that includes adipose tissue (fat cells), connective tissue, and muscle [3]

## 1.3 Cellulitis and Skin Abscess

Cellulitis is a rapidly spreading skin infection with ill-defined boarders that are limited to the dermis and subcutaneous tissues [5, 3] (Fig. 1.1). It is a clinical diagnosis with hallmark physical examination findings of unilateral skin erythema, warmth, tenderness, and swelling [1, 6]. Lymphangitis and regional lymphadenopathy may also be present [4]. The extremities, especially lower, are the most common locations for cellulitis to appear [4, 7]. Risk factors include any break in the skin barrier (e.g., trauma, even when seemingly quite trivial, such as scratches or scrapes, eczema, insect bites, tinea pedis, other chronic skin conditions), edema (including lymphedema), and other conditions resulting in venous stasis [1, 2]. The most common bacterial pathogen is *Streptococcus pyogenes*, but *Staphylococcus aureus* should also be considered, especially in cases of purulent cellulitis [1]. Routine blood work including blood and skin cultures and imaging is not recommended. Fewer than 1% of blood cultures are positive in

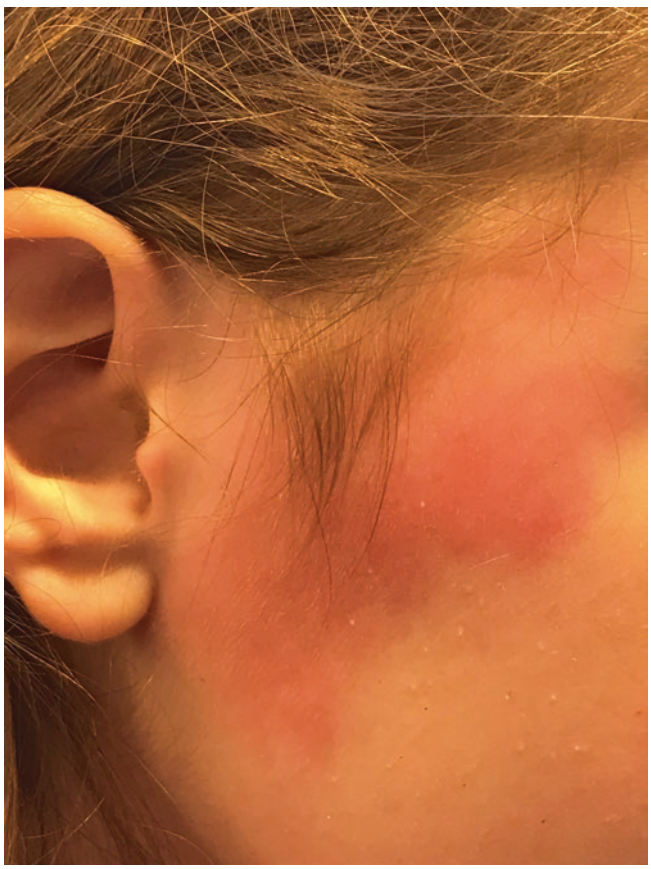

**Fig. 1.1** Facial cellulitis secondary to *S. pyogenes*. Note the ill-defined borders of erythema. (Image provided courtesy of Dr. Jennifer Nead)

pediatric patients, and fewer than 5% are positive in adult patients [4, 8–12] with uncomplicated cellulitis. In contrast, blood cultures should be considered in patients with bacterial skin and skin structure infections secondary to traumatic wounds, surgical wounds, aquatic injuries, ulcers, burns, or animal bite wounds and in immunosuppressed patients [4, 13]. Patients with cellulitis are typically treated for 5–10 days with antibiotics that include coverage for both *S. pyogenes* and MSSA [2, 4, 13]. The final duration of treatment depends on the patient's clinical response to antibiotics. MRSA coverage should be considered in patients with a past MRSA infection history or known colonization with MRSA, a family history of or close contact with an individual with known MRSA infections, injection or intravenous drug use, traumatic wound infections, purulent cellulitis, severe illness including systemic inflammatory response syndrome (SIRS), and clinical exams where it is difficult to distinguish cellulitis from early abscess formation [2, 4, 8, 13, 14]. Common antibiotic treatment regimens for non-purulent and purulent cellulitis are listed in ◘ Table 1.1. Cellulitis that fails to improve with appropriate antibiotic treatment should raise the suspicion for the presence of a coexisting abscess, deeper infection such as osteomyelitis, unusual pathogens, or alternative diagnosis. A differential diagnosis for cellulitis is listed in ◘ Table 1.2, and other important bacterial skin and skin structure infections are described in ◘ Table 1.3 (see also ◘ Figs. 1.2 and 1.3).

A tiny superficial collection of pus in the skin associated with the skin follicle is termed folliculitis. If the infection extends beyond the follicle, remaining superficial, it is termed a pustule (◘ Fig. 1.4). Pustules that become larger and deeper are referred to as boils or furuncles. They can enlarge to several centimeters in size. When several furuncles coalesce to form a deeper, more complex skin infection, they are termed carbuncles (◘ Fig. 1.5). A skin abscess is a localized cavity of pus that extends into the dermis and/or subcutaneous tissue.

The diagnosis of a skin and soft tissue abscess is made based on clinical findings [2, 4, 5]. A hallmark physical examination finding is the presence of a warm, tender, fluctuant skin mass with surrounding erythema [2, 4, 5] (◘ Fig. 1.6). If the pus cavity is close to the skin surface, then a pustule may be present [5] (◘ Fig. 1.7). The finding of fluctuance, a boggy sensation during palpation, distinguishes an abscess from cellulitis [5]. Fluctuance may be absent in cases of significant induration or deep abscess location [14]. Ultrasonography is a helpful diagnostic tool when physical examination findings are equivocal [13]. Purulent drainage should be sent for Gram stain and culture. *S. aureus* is the most common cause of skin and skin structure abscesses. A Gram stain will show gram-positive cocci in clusters [15]. Over the past few decades, MRSA strains have increased in prevalence to become a predominant cause of abscesses [2, 4, 5, 13] [► Call Out Box 1.1]. MSSA is, by definition, oxacillin-susceptible, while MRSA is oxacillin-resistant. Incision and drainage (I&D) remains the mainstay of abscess treatment [16]. The role of adjunctive antibiotics is controversial as

◘ **Table 1.1** Empiric antibiotic treatment recommendations for non-purulent cellulitis, purulent cellulitis, and abscess

| | |
|---|---|
| **Non-purulent cellulitis**<br>*Includes coverage against S. pyogenes and MSSA* | |
| **Outpatient**<br>Cephalexin<br>Dicloxacillin<br>Clindamycin | **Inpatient**<br>Cefazolin<br>Oxacillin or nafcillin<br>Clindamycin |
| **Purulent cellulitis**<br>*Includes coverage against S. pyogenes, MSSA, and MRSA* | |
| **Outpatient**<br>Clindamycin<br>Trimethoprim/sulfamethoxazole (TMP-SMX) or doxycycline *and* a β-lactam class antibiotic (e.g., penicillin, amoxicillin, cephalexin)<br>Linezolid<br>Note: Monotherapy with TMP-SMX or doxycycline does not provide adequate coverage against *S. pyogenes* | **Inpatient**<br>Clindamycin<br>Vancomycin<br>Linezolid |
| **Abscess**<br>*Includes coverage against MSSA and MRSA* | |
| **Outpatient**<br>Clindamycin<br>Trimethoprim/sulfamethoxazole (TMP-SMX)<br>Doxycycline (or minocycline)<br>Linezolid | **Inpatient**<br>Clindamycin<br>Vancomycin<br>Linezolid |

Prior to choosing empiric antibiotic coverage, always check local/regional antibiotic susceptibilities (e.g., antibiogram). In cases of purulent cellulitis and abscesses, wound culture results will help tailor antibiotic coverage

◘ **Table 1.2** Differential diagnoses for bacterial cellulitis

| Conditions | Diseases |
|---|---|
| Inflammatory | Arthritis, gout, bursitis |
| Dermatologic | Contact dermatitis, hypersensitivity reaction, drug reaction, and venous stasis dermatitis |
| Infectious | Cutaneous abscess, septic arthritis, necrotizing fasciitis, osteomyelitis, pyomyositis, erysipelas, staphylococcal scalded skin syndrome, ecthyma, erythema migrans, herpes simplex, herpes zoster and other viral, fungal, parasitic, and mycobacterial skin infections |
| Other | Insect bites, hematoma (traumatic or anticoagulation), deep venous thrombosis, and calciphylaxis[a] |

[a]A syndrome associated with calcification of blood vessels and skin necrosis in patients with uremia secondary to end stage renal failure

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**Table 1.3** Other important bacterial skin and skin structure infections

| Infection and definition | Common pathogen(s) | Clinical examination | Management |
|---|---|---|---|
| **Erysipelas:** Fig. 1.2<br>Sharply demarcated superficial skin infection of the upper dermis and superficial lymphatics<br>Most common in young children and older adults | *Streptococcus pyogenes* | Extremely erythematous and tender lesion that is raised and has distinct margins; common locations are the face and legs<br>Note: In contrast to cellulitis, erysipelas is a more superficial infection with raised and well-demarcated borders | Systemic antibiotics<br>If bullous erysipelas is present, include coverage against *Staphylococcus aureus* |
| **Impetigo:** Fig. 1.3<br>Highly contagious, localized superficial skin infection<br>Nonbullous impetigo is seen in 70% of cases, and bullous impetigo is seen in 30% of cases<br>Most common bacterial skin infection in children with peak incidence among children between ages 2 and 5 | Nonbullous impetigo: MSSA and/or *Streptococcus pyogenes*<br>Bullous impetigo: MSSA | Nonbullous impetigo: Maculopapular lesions progress to vesicles which rupture and leave superficial honey crusted lesions; common locations are face and extremities<br>Bullous impetigo: Large, flaccid bullae which rupture, oozing yellow fluid and leaving brown crusts; common locations are trunk, extremities, and intertriginous areas where the skin rubs together, such as the diaper area | Topical antibiotic such as mupirocin<br>Systemic antibiotic in outbreak settings or if lesions are numerous, widespread, or associated with large bullae<br>Consider MRSA coverage if unresponsive to first-line treatment |
| **Folliculitis**<br>Superficial skin infection in which hair follicle inflammation leads to a pus collection in the epidermis<br>More common in adolescents and adults | MSSA, MRSA<br>Less common: If hot tub exposure, consider *Pseudomonas* species | Erythematous papules/pustules at hair follicle sites; common locations are scalp, perioral, perinasal, neck, axillae, and extremities, especially the medial thighs | Warm compresses<br>Topical antibiotic such as mupirocin<br>Systemic antibiotic for severe cases |
| **Furuncle (boil)**<br>Folliculitis extends into the subcutaneous tissue where a small abscess forms<br>More common in adolescents and adults | MSSA, MRSA | Tender, firm/fluctuant, erythematous nodules with overlying pustules at hair follicle sites; common locations are scalp, buttocks, and extremities | Warm moist compresses<br>I&D (see abscess management in the text) |
| **Carbuncle**<br>Collection of adjacent furuncles connected by sinus tracts with multiple drainage points<br>More common in adolescents and adults | MSSA, MRSA | Organized group of adjacent furuncles with pus draining from multiple hair follicle sites | Warm moist compresses<br>I&D (see abscess management in the text) |
| **Necrotizing soft tissue infection**<br>Necrotizing infection involving any of the following: dermis, subcutaneous tissue, superficial fascia, deep fascia, or muscle | *Streptococcus pyogenes*<br>**or**<br>polymicrobial with gram-positive and gram-negative bacteria, including anaerobes | Tense edema adjacent to infected area, tenderness out of proportion to clinical exam findings, bruising, bullae, crepitus/subcutaneous gas, signs/symptoms of significant systemic illness including toxicity | Emergent evaluation for surgical debridement and initiation of broad-spectrum antibiotics are indicated<br>Broad-spectrum antibiotics (e.g., vancomycin plus piperacillin-tazobactam) |

their use may not improvement cure rates [4]. However, empiric antibiotics are recommended for severe or extensive disease including multiple abscess sites, the presence of signs and symptoms of systemic illness including SIRS, rapid worsening of clinical findings, underlying medical conditions including immunosuppression or comorbid conditions, extremes of age, abscesses located in difficult areas to drain (e.g., face, hands, genitals), coexisting septic phlebitis or extensive cellulitis, and lack of response to the initial I&D procedure [5, 8, 13, 14, 17]. When used, the antibiotic choice should include coverage against both MSSA and MRSA [18] [▶ Call Out Box 1.2].

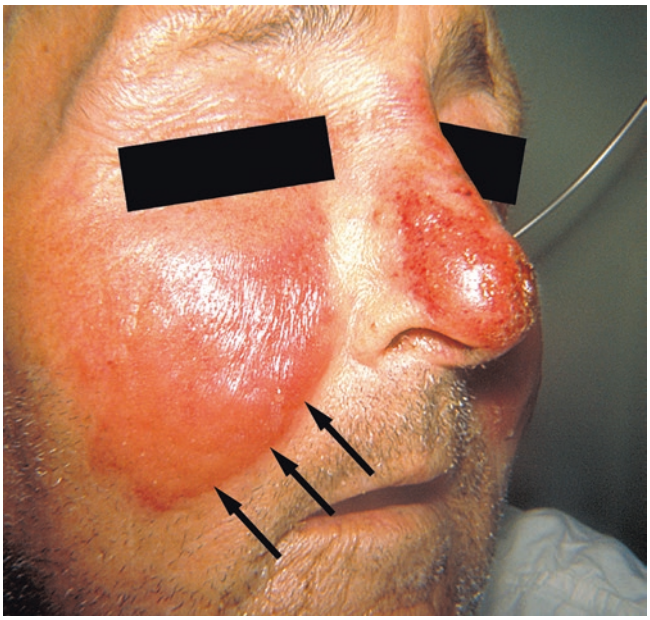

**Fig. 1.2** Facial erysipelas secondary to infection with *S. pyogenes*. Note the sharply defined raised borders (arrows). (Reprinted from the Centers for Disease Control and Prevention Public Health Image Library. Image ID#2874; ► https://phil.cdc.gov/phil/details.asp)

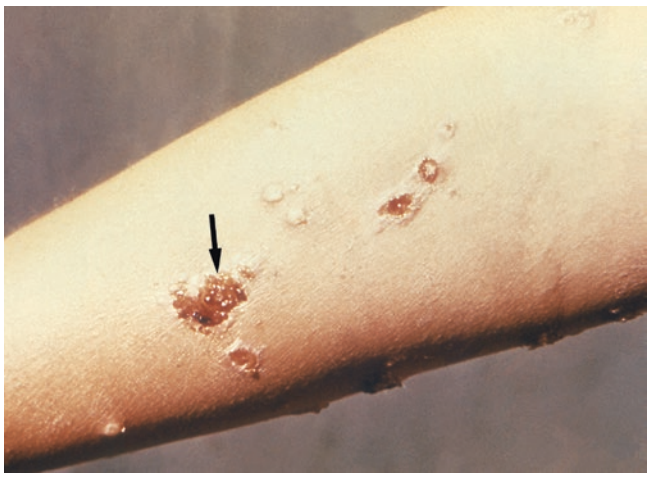

**Fig. 1.3** Impetigo secondary to infection with *S. pyogenes*. Note the appearance of honey-colored crusting (arrow). (Reprinted from the Centers for Disease Control and Prevention Public Health Image Library.Image ID#14927; ► https://phil.cdc.gov/phil/details.asp)

Indications for hospitalization in patients with bacterial skin and skin structure infections include failure of outpatient antibiotics, signs and symptoms of systemic illness including SIRS, rapidly progressing or extensive cellulitis or abscess, associated lymphangitis or septic phlebitis, and coexisting immunocompromised state or other comorbid conditions (e.g., diabetes, vascular or lymphatic abnormalities) [4, 5, 8]. The length of

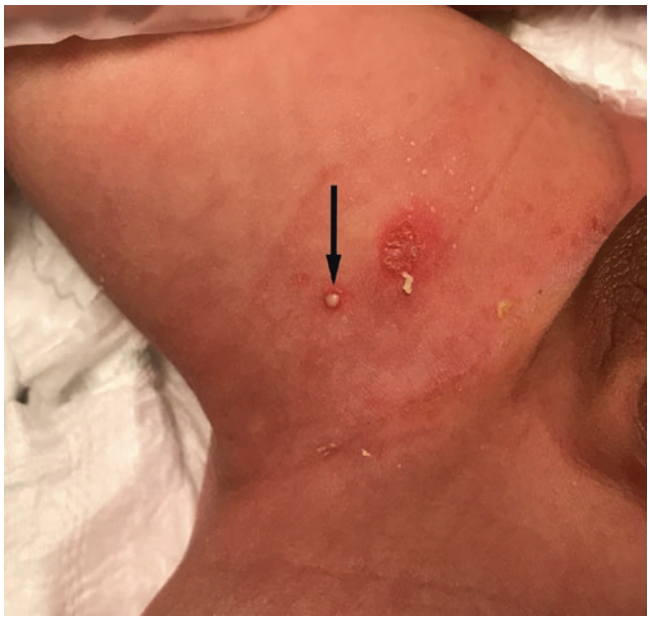

**Fig. 1.4** Superficial pustule caused by methicillin susceptible *Staphylococcus aureus* associated with minimal surrounding erythema. (Image provided courtesy of Dr. Jennifer Nead)

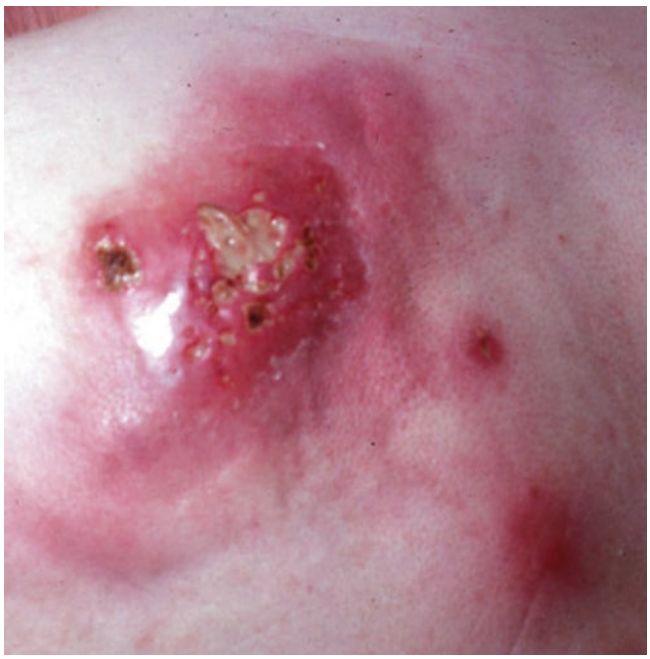

**Fig. 1.5** Staphylococcal carbuncle. (Image provided by Dr. Joseph Domachowske)

antibiotic treatment varies for hospitalized patients but is usually between 7 and 14 days. The therapeutic course is tailored based on the patient's clinical response to treatment [8].

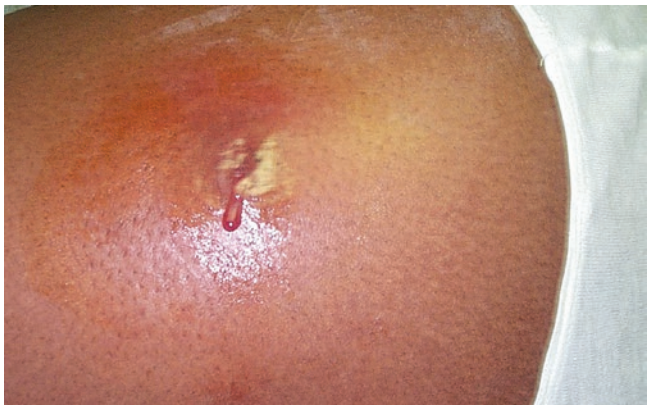

**Fig. 1.6** Left thigh abscess with spontaneous drainage of serosanguinous fluid, caused by methicillin-resistant *Staphylococcus aureus*. (Centers for Disease Control and Prevention (CDC) Public Health Image Library (PHIL). Image ID#7826; ► https://phil.cdc.gov/phil/details.asp)

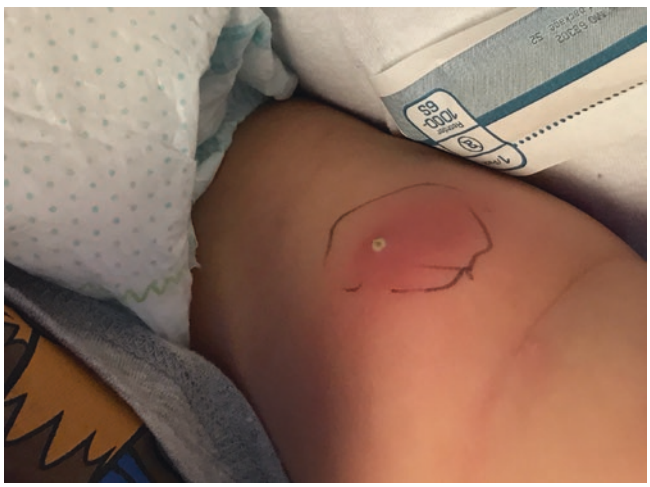

**Fig. 1.7** Cutaneous pustule with surrounding cellulitis. On palpation, fluctuance was noted, heralding the presence of a large, deep soft tissue abscess. An I&D was performed. Cultures of the infected material grew methicillin susceptible *Staphylococcus aureus*. (Image provided courtesy of Dr. Jennifer Nead)

**Call Out Box 1.1**
*Streptococcus pyogenes* is a common cause of cellulitis, but MSSA should also be considered. Most abscesses are caused by *Staphylococcus aureus*. Over the past few decades, MRSA has become a leading pathogenic cause of skin abscesses.

**Call Out Box 1.2**
A clinical exam finding of fluctuance distinguishes an abscess from cellulitis. It is common for cellulitis to develop into an abscess or for an abscess to have surrounding cellulitis. Cellulitis is treated with antibiotics. Abscesses are treated with I&D, and adjunctive antibiotics are only recommended in special circumstances such as coexisting cellulitis or severe infection.

## 1.4 Bite Wound Infections

MSSA, MRSA, and *S. pyogenes* are also common pathogens found in cat, dog, and human bite wound infections [19–21]; however, a recent bite injury should always raise concerns for other etiologies that come from the biting animal or human's oral flora [22]. Bite wound infections should always be considered polymicrobial in nature. Dog, cat, and human bite wound infections may grow four or more anaerobic and aerobic bacteria [7, 20, 22–24]. *Pasteurella* species are a common cause of cat and dog bite wound infections. *Pasteurella multocida* is frequently cultured from infections after bites from either animal [21, 24], while *Pasteurella canis* is typically only isolated from infected dog bites. *Eikenella corrodens* is a hallmark pathogen associated with human bite wound infections [19, 20, 23] [► Call Out Box 1.3]. These and other bacterial pathogens found in dog, cat, and human bite wound infections are listed in Table 1.4. Pathogens associated with uncommon and exotic animal bite wound infections can be found in Table 1.5. Most bite wounds occur in children and are typically due to cats, dogs, or humans [20, 23–25]. Dogs account for up to 90% and cats account for up to 10% of bites, respectively [25]. Infection is estimated to occur after 3–25% of dog bites, 20–50% of cat bites, and 10–30% of human bites [19, 22, 24]. If an infection develops within 12–24 h of a dog or cat bite, *P. multocida* is the most likely culprit [19, 26]. Infections following rodent and rabbit bites are rare [7]. Risk factors for the development of an infection include bites to the hands, feet, and genitals; bites causing puncture wounds (commonly seen from cats and birds); crush injuries from bites (common from horse bites); bites causing significant tissue destruction, edema, and poor perfusion; bites in areas with underlying venous/lymphatic compromise; comorbid conditions including diabetes, asplenia, and immunosuppression; bites near prosthetic joint hardware; bites in neonates and young infants; bites with delayed presentation to care (more than 6–12 h for arm and leg bites and more than 12–24 h for face bites); and surgically closed bite wounds [7, 19, 22, 25].

When obtaining a clinical history, details about the bite (e.g., timing and initial treatment) and the animal (e.g., type, wild vs. domesticated, rabies vaccination status) are important. Patients with bite wound infections may report fever and increased redness, pain, swelling, and purulent drainage at the bite site [22]. Clinical examination findings in bite wound infections include the bite injury characteristics (e.g., size, depth, shape, and nature of the tearing action leading to a laceration, puncture, or crush injury) and signs of infection

**Call Out Box 1.3**
The majority of bite wounds are caused by dogs, cats, and humans. *Pasteurella multocida* is a common cause of dog and cat bite wound infections, and *Eikenella corrodens* is associated with human bite wound infections. Most bite wound infections are left open to heal by secondary intention.

**Table 1.4** Bacterial pathogens associated with dog, cat, and human bite wound infections

| Source of the bite | Aerobic bacteria | Anaerobic bacteria | Other pathogen considerations |
|---|---|---|---|
| Dog | *Pasteurella* species<br>*Capnocytophaga canimorsus*<br>*Streptococcus* species<br>*Staphylococcus* species<br>*Neisseria* species<br>*Corynebacterium* species<br>*Moraxella* species | *Fusobacterium* species<br>*Bacteroides* species<br>*Porphyromonas* species<br>*Prevotella* species<br>*Cutibacterium* species<br>*Peptostreptococcus* species | Worldwide, the majority of human rabies cases occur after dog bites.<br>Although rare, transmission of *Leptospira* species and *Francisella tularensis* has been reported after dog bites |
| Cat | *Pasteurella* species<br>*Streptococcus* species<br>*Staphylococcus* species<br>*Moraxella* species<br>*Neisseria* species<br>*Corynebacterium* species<br>*Enterococcus* species<br>*Bacillus* species | *Fusobacterium* species<br>*Bacteroides* species<br>*Porphyromonas* species<br>*Veillonella* species<br>*Prevotella* species<br>*Cutibacterium* species | *Bartonella henselae* and *Bartonella quintana* may be transmitted via a cat scratch or bite.<br>Rarely, *Yersinia pestis* (cause of bubonic plague) and *Francisella tularensis* may be transmitted by cat bites |
| Human | *Eikenella corrodens*<br>*Streptococcus* species<br>*Staphylococcus* species<br>*Haemophilus* species | *Fusobacterium* species<br>*Peptostreptococcus* species<br>*Prevotella* species<br>*Porphyromonas* species<br>*Bacteroides* species | Viral infections can be transmitted by human bites if the bite results in bleeding. The biter is at much higher risk than the bitten when HIV, hepatitis B, or hepatitis C-contaminated blood enters the biters mouth |

**Table 1.5** Pathogens associated with uncommon or exotic animal bite wound infections[a]

| Animal bite | Bacteria isolated from wound infections[a] | Other considerations |
|---|---|---|
| Domestic birds including parrots, cockatiels, and parakeets | *Escherichia coli (most common)*<br>Others: *Salmonella* species, *Staphylococcus* species, *Pasteurella* species, *Proteus* species, *Bacillus* species, and *Klebsiella pneumoniae* | *Mycobacterium* species may be present in beaks, talons, and claws. If transmitted, indolent abscesses may develop.<br>*Chlamydophila psittaci* may be transmitted through bites and may lead to psittacosis.<br>Since birds often peck the ground, pathogens from soil or fecal contamination should also be considered |
| Horses and other equines including ponies, mules, donkeys, burros, and zebras | *Actinobacillus* species<br>*Streptococcus anginosus* and *Streptococcus mutans* may cause palpable gas in subcutaneous tissue similar to gas gangrene<br>Others: *Rhodococcus equi*, *Streptococcus equi zooepidemicus*, *Staphylococcus* species, *Yersinia* species, *Pasteurella* species, *Bacteroides fragilis*, *Campylobacter ureolyticus*, *Escherichia coli*, *Neisseria* species, and *Prevotella melaninogenica* | Rabies can be transmitted via horse bites if the animal is infected<br>*Burkholderia mallei*, the cause of glanders, is a disease that occurs in horses and mules. Humans acquire glanders via skin contact at the time of a horse or mule bite. Clinical manifestations include multiple pustular skin lesions, lymphadenopathy, suppurative lymphadenitis, sepsis, and death.<br>*Rhodococcus equi* is an important pathogen in immunocompromised patients that causes pneumonia and meningitis.<br>*Streptococcus equi zooepidemicus* (group c streptococcus) may also cause pharyngitis, adenitis, bacteremia, pneumonia, septic arthritis, osteomyelitis, endocarditis, meningitis, glomerulonephritis, and bacteremia |
| Monkeys | Pathogens causing wound infections after monkey bites are not well described. In general, pathogens are thought to be similar to those seen in human bite wound infections | Herpes simiae, the cause of herpes B virus infection, can be transmitted after a monkey bite. Clinical manifestations include life-threatening hemorrhagic meningoencephalitis |
| Pigs | *Flavobacterium* species, *Actinobacillus* species, and *Pasteurella aerogenes* | |
| Reptiles (in general) | *Salmonella* species and other enteric gram-negative bacteria, *Serratia* species, and anaerobes | |

(continued)

1

**Table 1.5** (continued)

| Animal bite | Bacteria isolated from wound infections[a] | Other considerations |
|---|---|---|
| Alligators/ Crocodiles | *Aeromonas hydrophila* is the most common reported pathogen.<br>Others: *Enterobacter agglomerans*, *Citrobacter koseri*, *Enterococcus* species, *Clostridium* species, *Proteus vulgaris*, and *Psuedomonas* species | |
| Iguana | *Serratia marcescens* is the most commonly reported pathogen | |
| Rodents including rats, guinea pigs, and hamsters | *Pasteurella multocida* is the most commonly reported pathogen | *Streptobacillus moniliformis* and *Spirillum minus* may be transmitted after rat bites, causing rat bite fever<br>Transmission of *Leptospira* species occurs when bite wounds come into contact with urine from infected animals or soil that is contaminated with infected urine<br>Tularemia resulting from transmission of F*rancisella tularensis* after hamster bites has been reported<br>Lymphocytic choriomeningitis virus may be transmitted after rodent bites.<br>Very rarely, hantavirus may be transmitted after rodent bites |
| Sharks | *Vibrio* species are the most commonly reported pathogens.<br>Others: *Aeromonas* species, *Proteus* species, *Klebsiella* species, *Clostridium freundii*, and *Enterococcus* species | |

Note: Empiric antibiotic treatment for uncommon and exotic animal bite wound infections should be based on the most likely pathogens, wound culture results, and consultation with a public health department official

[a]In cases of uncommon and exotic animal bite wound infections, pathogen information is limited to case reports or case series

consistent with cellulitis, purulent cellulitis, and/or abscess. Additional findings may include injury or infection involving tendons, muscles, bones, joints, and/or nerves. A thorough physical examination with special attention to deeper structures and the potential presence of foreign bodies such as teeth should always be performed [22, 25]. The depth of puncture wounds can be deceiving, resulting in the potential to miss injuries to bones, joints, and other deep structures. Tenosynovitis is the most common complication of bite wounds, but septic arthritis and osteomyelitis may also occur. Dog bites to the skull have even led to *Pasteurella multocida* meningitis in infants and toddlers [27].

The general approach to all bite wound infections is wound debridement if needed, copious wound irrigation, and antibiotic treatment. If purulent drainage is present, a sample should be collected for Gram stain and aerobic and anaerobic wound cultures. It is advisable to inform the microbiology lab that the cultures are from a bite wound [22]. This will ensure that appropriate transport and growth mediums are used to accurately identify anaerobic and more fastidious bacteria [19, 22]. If a *Pasteurella* species is present, then the Gram stain may show the characteristic gram-negative coccobacilli [27]. Blood cultures should be ordered if the patient is febrile or has signs and symptoms consistent with systemic involvement including SIRS [22]. Imaging is indicated when there is concern for underlying bone or joint injury (e.g., fractures), foreign bodies (e.g., teeth), or deep structure infections (e.g., osteomyelitis) [20, 23]. Some wounds may require debridement and surgical consultation. Bite wound closure is controversial, but most wounds should be left open to heal by secondary intention to prevent worsening infection [20]. Wound that is less than 12 h old, with no signs of infection, can be considered for primary closure [4, 20, 25].

Patients with underlying liver disease, solid organ transplant, or other immunosuppressed states are at increased risk of developing bacteremia from bite wound infections caused by *Pasteurella multocida* [27]. *Neisseria weaver* is an unusual isolate in the clinical microbiology laboratory, and when seen associated with a dog bite, wound infection suggests the presence of an underlying immunodeficiency, including asplenia [22]. Dogs bites infected with *Capnocytophaga canimorsus* can progress rapidly [23, 25]. Clinical manifestations include cellulitis, sepsis, disseminated intravascular coagulation, acute respiratory distress syndrome, meningitis, endocarditis, and multi-organ damage/failure [19, 23, 25]. The pathogen causes high morbidity and mortality in elderly patients and patients with a history of alcoholism, severe liver disease, asplenia, chronic lung disease, and other diseases that result in immunocompromised states [22, 23, 25].

In general, amoxicillin-clavulanate (outpatient treatment) or ampicillin-sulbactam (inpatient treatment) provides excellent coverage for the aerobic and anaerobic pathogens causing dog, cat, and human bite wound infec-

tions [4, 20]. Other options include a second- or third-generation cephalosporin (e.g., cefuroxime) plus an antibiotic with anaerobic coverage (e.g., clindamycin) [4]. MRSA coverage should be considered for severe bite wound infections and in patients with MRSA infection or colonization history [20]. Consultation with an infectious disease specialist and/or a local health department official is recommended for uncommon and exotic animal bites. Ultimately, empiric antibiotic treatment should be based on the known pathogens present in the biting animal's oral flora. Cellulitis and abscess are usually treated for between 5 and 10 days [20]. If bacteremia is present, antibiotic treatment is typically 10–14 days in length. Deep infections with joint and bone involvement require longer treatment courses. Ultimately, the duration of antibiotic treatment depends on the extent of the infection, the isolated pathogens, and the patient's clinical course. Hospitalization is recommended for patients with severe or deep wound infections or who meet criteria listed earlier for inpatient treatment of cellulitis or abscess.

Antibiotic prophylaxis to prevent bite wound infections is not routinely recommended for immunocompetent patients, especially if there is a low risk for infection. Bite wound antibiotic prophylaxis is generally recommended for patients with immunocompromising conditions or other comorbidities. Administration of amoxicillin-clavulanate for 3–5 days following the bite is prudent under these circumstances [4, 20].

It is important to review tetanus vaccination history anytime a wound is assessed. For clean, minor wounds, if a patient has not completed primary tetanus immunization (i.e., fewer than 3 doses) or it has been more than 10 years since the last dose, a tetanus toxoid containing vaccine is indicated [4, 20, 25]. Tetanus immune globulin is not needed [4, 25, 28]. For all other wounds, if a patient has not completed primary tetanus immunization, then both tetanus immune globulin and a tetanus toxoid vaccine are indicated [4, 20, 25]. If a patient has completed primary tetanus immunization but it has been more than 5 years since the last dose was given, a booster dose of tetanus toxoid vaccine is indicated [4, 20, 25].

It is also important to ascertain the rabies vaccination status of any animal that bites a person. In general, rabies postexposure prophylaxis is recommended for bites inflicted by wild animals, unvaccinated pets, and rabid or rabid-appearing animals [20, 23, 29]. Rabies postexposure prophylaxis includes (1) administration of human rabies immune globulin (infiltrate the wound and administer the remaining immune globulin via intramuscular injection at a distant site) and (2) administration of rabies vaccine on days 0, 3, 7, and 14 [29]. In the United States, routine rabies prophylaxis is not indicated following bites of healthy-appearing dogs and cats [29] if the animal can be captured and observed for 10 days [29]. Immediate vaccination is recommended following bat, raccoon, skunk, fox, and most other carnivore bites as these animals should be considered to be rabid unless proven otherwise [29]. Consultation with a public health department expert is recommended following horse, rodent, rabbit, and other mammal bites (CDC) since postexposure prophylaxis after such encounters is rarely necessary [29]. It is advisable to be familiar with local and state laws as most areas require reporting of dog and other animal bites [25].

## 1.5 Wound Infections Following Aquatic Injuries and Exposures

*S. aureus* and *S. pyogenes* remain common pathogens in wound infections resulting from aquatic injuries [30]. However, pathogens specific to the aquatic exposure (e.g., seawater, brackish water, freshwater) should also be considered. This section highlights skin and skin structure wound infections caused by *Vibrio species*, *Aeromonas species*, and *Mycobacterium marinum*. In general, injuries or wounds with aquatic exposures should be treated with broad-spectrum antibiotics that cover *S. aureus*, *S. pyogenes*, and the pathogens unique to the specific exposure [30]. The duration of antibiotic treatment will depend on the type of injury and the extent of the wound infection.

Marine *Vibrio* species thrive in warm water with high salt concentrations [31]. Consequently, they are found worldwide in seawater and brackish waters [30–32]. *Vibrio vulnificus*, *Vibrio parahaemolyticus*, *Vibrio alginolyticus*, and *Vibrio damsela* have been identified as pathogens causing serious wound infections in patients with underlying risk factors including chronic hepatitis, liver cirrhosis, alcoholism, hemochromatosis, diabetes, cancer, chronic renal failure, and other immunosuppressive conditions [30, 31, 33]. In particular, *V. vulnificus* is an extremely invasive and virulent bacterium that causes more deaths than other marine *Vibrio* species [31, 33, 34]. Skin and soft tissue infections caused by *V. vulnificus* are regularly reported after natural disasters involving flooding with saltwater, such as occurred in 2005 in the aftermath of Hurricane Katrina [33, 35, 36].

Marine *Vibrio* species also cause infections after other types of injuries to the skin involving sharp objects in or taken from saltwater sources. Activities that lead to cuts in the skin during recreational or occupational activities where open wounds are exposed to seawater such as stepping on a seashell, swimming into coral, or shucking oysters may all lead to *Vibrio* species infections [30–33]. High-risk patients who develop wound infections from *V. vulnificus*, such as those with chronic liver disease, typically progress rapidly from cellulitis to widespread tissue necrosis [30, 31, 33]. Additional disease manifestations include necrotizing fasciitis and/or myositis, osteomyelitis, sepsis, and death [4, 33]. Management includes emergency surgical debridement of necrotic and infected tissue and initiation of broad-spectrum antibiotics while awaiting the results of wound and blood cultures [30, 31, 37]. Antibiotic regimens that provide coverage against *V. vulnificus* include doxycycline plus ceftriaxone or cefotaxime, or monotherapy with either ciprofloxacin or levofloxacin [4, 30, 33]. In patients with underlying risk factors, reported mortality rates from marine *Vibrio* species wound infections are between 25% and 33% in patients who have early and aggressive debridement and 66–100% in patients who do not [32] [► Call Out Box 1.4].

1

**Call Out Box 1.4**
Patients with underlying chronic liver disease are at increased risk for infections caused by *Vibrio vulnificus*. Soft tissue infections spread rapidly, causing extensive tissue necrosis over a very short period of time. Aggressive surgical debridement with partial limb amputations can be life-saving. Mortality rates are high.

*Aeromonas species*, including *Aeromonas hydrophila*, are found worldwide in warm brackish water and freshwater [38, 39]. Other reported sources include sewage, soil, and tap water [32, 38]. Patients typically become infected with *Aeromonas* species through areas of skin breakdown during occupational or recreational activities [38]. After natural disasters, such as the Indian Ocean earthquake on December 26, 2004, and tsunami that affected large portions of coasts in Thailand, Malaysia, and Indonesia and surrounding areas, reports of infection with *Aeromonas* species, like reports of *V. vulnificus* infection, are common [36, 38]. In addition, given the more ubiquitous presence of *Aeromonas* species, nosocomial infections involving surgical and burn sites have been reported [38]. Risk factors, clinical manifestations, and management of severe skin and skin structure infections from *Aeromonas species* and *V. vulnificus* are very similar [32, 38, 39]. Mortality rates associated with *Aeromonas* species soft tissue infections are substantial, but somewhat lower than that seen with *V. vulnificus* infections [38, 40].

*Mycobacterium marinum* is a nontuberculous mycobacterium found in both freshwater and saltwater [34]. Common sources of human exposure include non-chlorinated swimming pools, aquariums, and infected fish [34, 41]. *M. marinum* is acquired through areas of skin breakdown during recreational or occupational activities such as handling fish or cleaning aquarium tanks [34]. Since the incubation period ranges from 2 weeks to 2 months, patients may not remember minor skin injuries that might have led to an exposure [34]. In contrast to infections caused by *V. vulnificus* and *A. hydrophila*, *M. marinum* causes indolent and superficial skin structure infections. Classically, a single granulomatous nodule appears at the inoculation site. The nodule then develops ulceration that may express purulent drainage [30, 39, 42]. Complications of *M. marinum* skin infections include tenosynovitis, bursitis, osteomyelitis, sclerokeratitis, and disseminated infection, especially if patients are left untreated or are immunocompromised [30, 34, 39]. Stains and cultures for acid-fast bacilli should be sent from the granuloma or its drainage [30]. The organism grows relatively quickly compared to other *Mycobacterium* species, requiring 1–2 weeks for results to become available. Polymerase chain reaction (PCR)-based testing for *M. marinum* can be requested, although depending on the laboratory, the turnaround time for results may be in the same range [30]. Patients infected with *M. marinum* may show a response to purified protein derivative (PPD), the antigen used for intradermal tuberculin skin testing [41]. *M. marinum* is usually susceptible to rifampin, rifabutin, ethambutol, clarithromycin, sulfonamides, or trimethoprim-sulfamethoxazole [38, 41, 42]. Specific treatment regimens are not well defined, but in general two agents are used (e.g., clarithromycin plus rifampin) until symptoms have been resolved for 1–2 months [42]. Most infections will require 3–4 months of treatment [42].

Other aquatic pathogens causing skin and skin structure infections include *Streptococcus iniae*, *Erysipelothrix rhusiopathiae*, *Shewanella* species, *Chromobacterium violaceum*, gram-negative enteric bacteria, and *Pseudomonas aeruginosa* [1, 7, 30, 38].

## 1.6 Less Common Pathogens in Skin and Skin Structure Infections

In addition to bite wounds and wounds exposed to water and soil, gram-negative bacteria and anaerobes should also be considered as causes of skin and skin structure infections in patients with traumatic wounds, surgical wounds, diabetes mellitus, chronic liver disease, chronic kidney disease, cancer, transplantation, or infection with human immune deficiency virus [1, 8]. *Escherichia coli*, *Enterobacter* species, *Klebsiella* species, *Haemophilus influenzae*, *P. aeruginosa*, *Enterococcus* species, anaerobes, *Nocardia* species, and nontuberculous mycobacteria have all been described as causes of cellulitis and/or abscesses [1, 3, 6, 43]. If a patient is severely ill or immunocompromised, then initial broad-spectrum intravenous antibiotics that include coverage against resistant gram-positive bacteria (e.g., MRSA), resistant gram-negative bacteria (e.g., *P. aeruginosa*), and anaerobes are recommended [4, 8].

## 1.7 Clinical Clues to Underlying Immunodeficiency

An underlying primary or acquired immunodeficiency should be suspected in patients with necrotizing fasciitis whose histories are negative for underlying medical conditions or significant predisposing events such as trauma [7, 44]. Recurrent skin and skin structure infections are common in adults with structural defects like pilonidal cysts or comorbid diseases such as diabetes. However, recurrent infections and infections that require longer courses of antibiotic treatment than typically expected should raise suspicion for an underlying immunodeficiency.

Chronic granulomatous disease (CGD) should be considered in children who have a single cutaneous abscess that cultures positive for an unusual pathogen such as *Serratia* species [45] and in those with severe, recurrent or stubborn *S. aureus* skin infections. Patients with CGD typically have severe recurrent abscesses of the skin, lung, liver, and perirectal area caused by catalase-producing bacteria and molds [45]. The finding of ecthyma gangrenosum in a previously healthy child may also be a clue to underlying CGD [7]. At first, an ecthyma lesion may resemble impetigo, but it then becomes necrotic and ulcerates leaving a black eschar [6, 7].

Recurrent *S. aureus* skin and skin structure infections such as abscesses and furunculosis should also raise suspicion for possible hyper-IgE syndrome [7, 46]. Patients with hyper-IgE syndrome usually present with a classic triad of eczema, recurrent cutaneous and lung abscesses, and very high IgE levels. Dental and skeletal problems (e.g., scoliosis) are also seen in patients with autosomal dominant stat-3 deficiency, the most common genetic form of hyper-IgE syndrome [46].

Recurrent *S. aureus* skin infections are very common in young children, while only 20 new cases of CGD and fewer than 10 new cases of autosomal dominant stat-3-deficient hyper-IgE syndrome are diagnosed each year in the United States. The rare genetic immune deficiencies are important to consider during the evaluation of recurrent skin and soft tissue infections, but the vast majority of the patients do not require detailed testing. In cases where the child is failing to thrive, has had deep tissue infections, or has a positive family history for an immunodeficiency, genetic testing to evaluate for CGD and/or hyper-IgE syndrome is indicated.

## Case Study

### Practical Examples

A 10-year-old male with a medical history of eczema is playing outdoors and gets a mosquito bite on his leg. He scratches at the bite until it bleeds. A few days later, he develops redness, swelling, warmth, and tenderness at the bite site. He is seen by his medical provider and diagnosed with cellulitis and treated with a 7-day course of oral cephalexin (a first-generation cephalosporin antibiotic). The provider explains that any breakdown in the skin barrier will increase the risk for infection. He also explains that a skin culture is not needed because purulent drainage is not present. The cephalexin provides empiric coverage for *Streptococcus pyogenes* and MSSA, the most common bacterial causes of cellulitis.

A 26-year-old female with a history of intravenous (IV) drug use presents to a walk-in clinic with the complaint of a "spider bite." The provider examines the site and finds an erythematous, warm, tender, fluctuant nodule with surrounding cellulitis under the skin. An incision and drainage (I&D) procedure is performed. The drained material (all of it, not just a swab from the infected area!) is sent to the laboratory with a request for a Gram stain and culture [► Call Out Box 1.5]. The patient is diagnosed with an abscess and surrounding cellulitis. The Gram stain reveals gram-positive cocci in clusters. Since the patient has a history of IV drug use, the provider prescribes oral clindamycin for 5 days. The patient comments, "My friend just had an abscess and only needed an I&D. I don't get why I need to take an antibiotic!" The provider explains that the patient is correct that the mainstay of abscess treatment is I&D but the presence of cellulitis in addition to the abscess requires antibiotic treatment. Two days later, the wound culture results were positive for MRSA, susceptible to clindamycin. The patient showed signs of clinical improvement.

A 3-year-old girl is playing with her neighbor's cat. She pulls the cat's tail and it bites her on the arm. The girl's mother washes the bite wound with soap and water, puts a bandage on it, and tucks the child into bed. The next morning, the girl has a fever of 38.8 °C, and the bite site is red, swollen, painful, and draining pus. The girl is seen at the local emergency department, where a provider collects swabs of the purulent drainage for culture, irrigates the bite wound, orders intravenous ampicillin-sulbactam, and admits her to the hospital for treatment of purulent cellulitis following a cat bite. The wound culture grows *Pasteurella multocida*. The mother asks, "How did my daughter develop this infection so quickly?" The provider explains that the cat bite resulted in a deep puncture wound. As a result, bacteria from the cat's mouth reached the subcutaneous tissue and were trapped, making it easy for an infection to develop despite the first aid she received immediately following the bite. The provider explained that it is classic for *P. multocida* to cause a rapidly progressing bite wound infection, usually within 12–24 h after a bite.

A 65-year-old man with poorly controlled type 2 diabetes mellitus takes a trip to Florida. While swimming in the ocean, he cuts his leg on a piece of coral. The cut seems minor, but within several hours, a rapidly progressing cellulitis develops. By the time he reaches a local emergency department, the cellulitis has progressed to a necrotizing skin and soft tissue infection. He receives broad-spectrum intravenous antibiotics and undergoes emergency surgical excision of the infected and necrotic tissue. Despite the aggressive management, the man dies from sepsis that night. Wound and blood cultures grow *Vibrio vulnificus*. The intensive care nurse who cared for the man postoperatively asks the surgeon, "Do people usually die from this infection?" The surgeon explains that *V. vulnificus* is a virulent saltwater pathogen associated with high mortality rates, especially among patients with underlying risk factors like diabetes mellitus.

A 20-year-old man is involved in a freshwater lake boating accident sustaining deep lacerations and crush injuries to his right leg, largely from the boat's propeller. Bleeding is controlled prior to the arrival of the first responders. At the trauma center, the wounds are irrigated with copious amounts of fluid, and broad-spectrum intravenous antibiotics are administered. The surgical trauma team notes extensive damage to muscle, blood vessels, and nerves and works to restore perfusion to the injured tissue. The next day, the man is brought back to the operating room so the wound can be explored further. Perfusion to the injured tissue appears only partially successful. Several areas of nonviable tissue are debrided. A modest amount of purulent exudate is now present in the wound. Several pieces of debrided tissue are sent to the microbiology laboratory for culture. A Gram stain of the sample shows 4+ gram-negative rods. The following day, the man develops fever to 40 °C with several episodes of hypotension. Blood cultures are collected, and the man is brought back to the operating room for further wound exploration. The surgeon notes widespread infection, with severely compromised tissue perfusion. A decision is made to perform a transfemoral (above the knee) leg amputation. Blood and wound cultures both grow *Aeromonas hydrophila*. Two days later, the man has defervescence, the residual limb surgical amputation site appears healthy, and discussion centered on the planned rehabilitation strategy has begun.

1

**Call Out Box 1.5**
Draining an abscess serves both therapeutic and diagnostic purposes. Evacuation of the infected material is often curative. Cultures performed by the microbiology laboratory are most often positive allowing for pathogen identification and antimicrobial susceptibility testing to be performed. Whenever material is collected by I&D or other procedure, send as much of the sample to the laboratory as possible. Collecting and submitting a swab from the infected area and discarding the infected material should be avoided.

## 1.8 Exercises

Please refer to the supplementary information section for answers to these exercises.

**Fill in the blanks**

1. _____is the most common bacterial pathogen causing abscesses. Over the past decade, there has been a significant increase in _____strains.

2. _____is a pathogen found in both seawater and freshwater. A few weeks to months after a cutaneous abrasion or laceration is exposed to the organism in water, insidious skin and soft tissue lesions develop. Hallmark clinical findings are granulomatous skin lesions that drain purulent material.

3. _____and_____are aquatic pathogens that cause rapidly progressing skin and skin structure infections in patients with underlying co-morbid or immunosuppressed conditions. Often, such patients present with cellulitis that rapidly progresses to necrotizing infections involving the fascia and muscles. If left untreated, there is an extremely high mortality rate.

**True or False**

4. _____MRSA is the most common pathogen causing cellulitis.

5. _____Pasteurella species are the most frequent pathogens in dog and cat bite wound infections.

6. _____Streptococcus pyogenes is a bacterial pathogen that is routinely cultured from abscesses.

7. _____Eikenella corrodens is a bacterial pathogen that causes infection following human bites.

8. _____For non-penicillin allergic patients, amoxicillin-clavulanate is the preferred oral treatment for cat, dog, and human bite wound infections.

## 1.9 Summary

Skin and skin structure infections including cellulitis and abscesses are common reasons for presentation to medical care in the outpatient and inpatient settings. *S. pyogenes* and MSSA primarily cause cellulitis, and *S. aureus* is the most common cause of abscesses. Over the past few decades, MRSA has increased in prevalence and in some locations is now the leading cause of abscesses. Less common pathogens including gram-negative bacteria and anaerobes should be considered in patients with skin and soft tissue infections associated with bite wounds, aquatic injuries or exposures, trauma, surgical wounds, immunosuppression, and comorbid conditions like diabetes. Recurrent skin and skin structure infections may be a clue to an underlying immunodeficiency, especially in pediatric patients.

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## Further Reading

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## Related Links to Journals, Books, and/or URLS

IDSA Practice Guidelines: http://www.idsociety.org/IDSA_Practice_Guidelines/.
AAP Red Book Report on the Committee on Infectious Diseases: https://redbook.solutions.aap.org/.
Comprehensive microbiology reference for common, uncommon, and exotic animal bites: https://www.ncbi.nlm.nih.gov/pubmed/21482724.
CDC Rabies information: https://www.cdc.gov/rabies/index.html.

# Febrile Exanthems of Childhood

## A Child with Fever and Rash

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2

As a presenting problem, fever and rash during childhood have an extensive list of possible causes. The goal of this chapter is review the most classic of these illnesses. Although they have disparate etiologies, febrile exanthems of childhood historically have been grouped together because of the prominent features they share: fevers and rashes and physical signs that parents can readily identify, although not always accurately. The clinical and epidemiological significance of febrile eruptions has changed during the past 50 years due to immunizations, technical advances in pathogen identification, and evolution of the causative organisms. For example, varicella infection was once commonplace, but its subsequent decline in prevalence after the introduction of universal childhood vaccination has made it more difficult for parents and providers to diagnose visually when it does occur. An illness like scarlet fever which was once feared for its potential life-threatening complications, only rarely results in significant morbidity or mortality today largely due to evolution of the causative organism, with loss of virulence over time.

The original classification of the most common febrile exanthems of childhood listed six illnesses in numerical order [▶ Call Out Box 2.1] [1]. First Disease is measles, Second Disease is scarlet fever, Third Disease is rubella, Fourth Disease is Filatov-Dukes' disease, Fifth Disease is erythema infectiosum, and Sixth Disease is roseola or exanthema subitum. Filatov-Dukes' disease was described in 1900, but is no longer considered to be a distinct entity and is only listed here for historical purposes [2]. With the lone exception of Fifth Disease, the numerical classification is no longer used to describe these illnesses. Two other classic febrile exanthems that are typically seen during childhood that will be discussed in detail include hand, foot, and mouth disease and varicella (chicken pox). The subtitle heading for each of the descriptions of each of these febrile rash illnesses will include other names that are used synonymously, with the most commonly understood name listed first.

## 2.1 Measles, Rubeola

Prior to the 1963 licensure and widespread use of measles vaccine in the USA, nearly all children developed measles infection by mid-adolescence. Most were infected during preschool age or shortly thereafter. At the time, there were an estimated 3 million cases and 500 measles associated deaths in the USA annually. By 1982, there were only 1497 cases, the lowest ever reported in the USA at the time, and in 2000, the US Centers for Disease Control and Prevention (CDC) declared the USA measles-free. The declaration indicated a lack of endemic measles cases, not an absence of disease. Measles virus continues to circulate globally, and imported cases continue to be problematic especially when an imported case enters a community where immunization rates are suboptimal. Unfortunately, parental hesitancy to routine immunization practices has led to new pools of susceptible children, so each newly imported measles case typically leads to secondary cases, often with outbreaks.

Measles is transmitted from person to person by the airborne route, explaining why it is one of the most contagious human infections known. Measles also has a very high attack rate, underscoring the importance of maintaining high immunization rates across the population [▶ Call Out Box 2.2]. Prior to the widespread control of the disease through ongoing vaccination programs, measles had a peak incidence during late winter and spring. After a susceptible individual is exposed to measles, there is 7- to 21-day incubation period before the patient develops high fever, cough, coryza, and conjunctivitis [▶ Call Out Box 2.3]. Careful inspection of the buccal mucosa may reveal the presence of Koplik spots. These fleeting bluish-gray or white lesions are pathognomonic for measles infection [▶ Call Out Box 2.4] [2]. The

**Call Out Box 2.1**
**The six classic childhood exanthems**

| Numbered disease | Names | Etiologic agent |
|---|---|---|
| First Disease | Measles, rubeola | Measles virus |
| Second Disease | Scarlet fever | *Streptococcus pyogenes* |
| Third Disease | Rubella, German measles | Rubella virus |
| Fourth Disease | Filatov-Duke's disease | Obsolete classification |
| Fifth Disease | Erythema infectiosum | Human parvovirus B19 |
| Sixth Disease | Roseola, exanthema subitum | Human herpes virus 6 |

**Call Out Box 2.2**
The attack rate of an infectious disease is a biostatistical measure used to estimate how quickly an infection spreads to those who are susceptible if exposed. It can be useful to predict the number of new cases to expect during an outbreak situation. An attack rate is determined by dividing the number of new cases identified among those who are susceptible (or unvaccinated) by the total number of susceptible individuals.

**Call Out Box 2.3**
Remember that measles is a respiratory tract infection. In addition to fever and rash, look for its classic four signs and symptoms that start phonetically with a hard /k/ sound: COUGH, CORYZA, CONJUNCTIVITIS, and KOPLIK'S SPOTS.

**Call Out Box 2.4**
"Pathognomonic" indicates that a sign, symptom, or collection of both is highly characteristic for a particular disease. While the finding falls short of "diagnostic," the term is sometimes used with that degree of conviction.

**Call Out Box 2.5**
The term "morbilliform" means measles-like. When the term is used, it is generally understood to indicate the generalized presence of dark red macules and papules that coalesce.

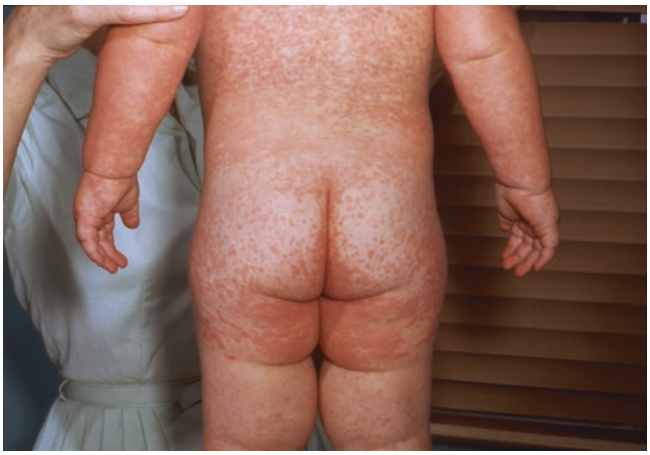


**Fig. 2.1** A child with measles. Note the maculopapular nature of the race with areas of coalescence on the upper thighs and buttocks. Image obtained from the Public Health Image Library number 4497; Content Provider is the Center for Disease Control and Prevention

measles rash begins on the face and spreads caudally and outwards to the hand and feet. It begins as discrete dusky erythematous maculopapules that coalesce as the illness progresses [▶ Call Out Box 2.5] (Fig. 2.1). At the peak of illness, headache and photophobia can be prominent complaints. In uncomplicated disease, resolution of the fever and rash occurs gradually over the following week. Common complications of measles include otitis media and pneumonia. Measles encephalitis is uncommon, but when it does occur, it is life-threatening. Complications from pneumonia and encephalitis account for the majority of measles-associated deaths. A more insidious neurologic complication following measles infection known as subacute sclerosing panencephalitis (SSPE) is ultimately lethal [3].

There is no specific treatment available for measles infection; however children from developing countries and children with severe measles should be treated with vitamin A supplementation. Administering antipyretics and encouraging good hydration provide some symptomatic relief [3, 4]. Cases of suspected or confirmed measles should be quarantined immediately to reduce the potential for spread of this highly contagious infection. Unimmunized individuals who have had contact with an index case of measles may benefit from receiving measles vaccine if it is administered within 72 h of the exposure.

## 2.2 Scarlet Fever

*Streptococcus pyogenes*, the bacteria that causes scarlet fever, was first recognized in 1884 by Friedrich Loeffler, a German physician who isolated the organism from throat cultures he collected from his patients. Humans are the only known natural host of *S. pyogenes*. Transmission of the bacteria from person to person occurs primarily via respiratory secretions, but may also occur via contaminated food and surfaces such as eating utensils, beverage containers, and toothbrushes. Acute tonsillopharyngitis, or "strep throat," is the most common manifestation of *S. pyogenes* infection. A patient is diagnosed with scarlet fever when presenting with streptococcal pharyngitis and an associated distinctive skin rash. Typical physical examination findings include any combination of fever with tonsillar enlargement, tonsillar and/or pharyngeal exudate, tender anterior cervical lymph nodes, and palatal petechiae. Examination of the tongue may reveal a whitish coating over edematous papillae, giving it the appearance of a "strawberry tongue."

A subset of children with streptococcal pharyngitis will develop scarlet fever. The scarlet fever rash becomes apparent during day one or two of the illness, beginning on the trunk and spreading outwards toward the extremities, sparing the palms and soles (Fig. 2.2). The rash has a sandpaper-like feel, best appreciated by the examiner by rubbing the patient's chest or abdomen with an open hand. It is one of the few rashes best appreciated by touch, and not observation. The flexural creases of the arms and legs may show an accentuated pattern of eruption, and the patient's cheeks usually have a flushed appearance. The rash typically resolves over the following 4–5 days. Significant desquamation at the resolution of the rash can appear alarming, but is harmless. *S. pyogenes*

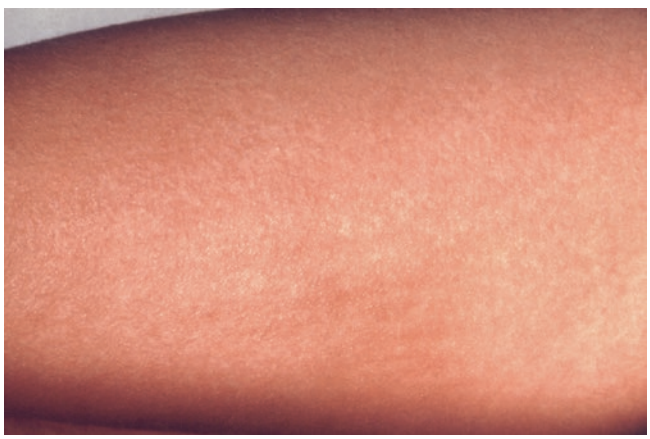


**Fig. 2.2** The rash of scarlet fever on the volar aspect of the arm. On palpation the fine nature of the papules feels like sandpaper. Image obtained from the Public Health Image Library number 5163; Content Provider is the Center for Disease Control and Prevention

**Call Out Box 2.6**
*Arcanobacterium haemolyticum* should be considered as the possible cause of a scarlet fever-like illness when diagnostic laboratory studies fail to implicate *S. pyogenes*. Most clinical microbiology laboratories will look for it in a throat culture, but only if requested specifically to do so.

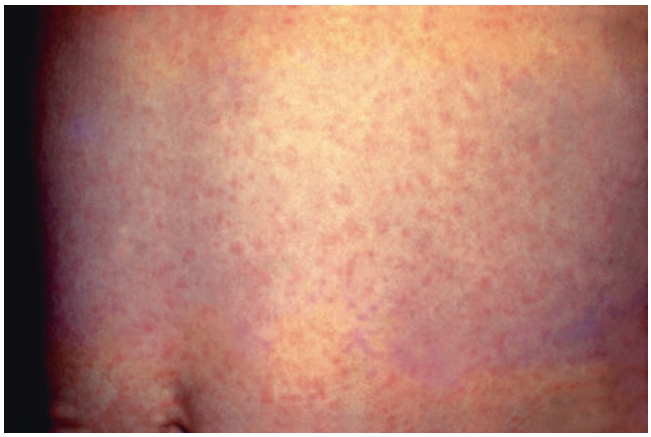
exotoxins have been implicated as the trigger for the scarlet fever rash.

Classic scarlet fever is a clinical diagnosis, but there are some illnesses that do appear similar [▶ Call Out Box 2.6]. As such, diagnostic testing to confirm that the infection is caused by *S. pyogenes* is recommended. Appropriate testing includes a throat culture or a *S. pyogenes* antigen detection assay. Once the diagnosis is confirmed, treatment with oral penicillin or amoxicillin is preferred. Several appropriate alternatives are available to treat the penicillin allergic patient.

## 2.3 Rubella, German Measles

Rubella, or German measles, was initially dubbed the Third Disease. It was first described in the German medical literature in 1814 [5] as a respiratory infection similar to, but milder than measles. Community transmission of rubella infection occurs by respiratory droplets, not via the airborne route, explaining why the infection has a lower attack rate than measles. After exposure, there is a 2-week incubation period. Rubella is a mild illness. Those who become symptomatic develop fever with rash that typically lasts fewer than 5 days. Like the rash seen with measles, the rubella rash appears first on the face, spreading to the trunk, and then the arms and legs. The "rose-pink" maculopapular rash is not as intense as measles and does not coalesce [2] (◘ Fig. 2.3). Bathing in hot water may intensify the color of the rash. Cervical lymphadenopathy, both before and after the onset of the rash, is common and may persist for a number of weeks. Although young children do not typically exhibit a classic prodrome, older children and adults may develop several days low-grade fever, malaise, eye pain, headache, and/or respiratory symptoms prior to the appearance of the rash [5, 6]. Complications of rubella infection are rare in children but do include encephalitis and post-infectious thrombocytopenic purpura [5, 6]. Adolescent and adult females who develop rubella infection have an increased risk for developing post-infectious arthralgias and arthritis that can become quite disabling.

Congenital rubella syndrome is the single most feared complication of rubella infection and was the rationale for the development and maintenance of a robust immunization program against the infection. Approximately 85% of infants born to women who are infected with rubella virus during the first trimester of pregnancy are born with features of congenital rubella syndrome. The last rubella epidemic in the USA occurred between 1964 and 1965 and included at least 12.5 million infections. As a result of that epidemic, more than 20,000 infants were born with congenital rubella syndrome.



◘ **Fig. 2.3** Shown is the truncal rash of a child with rubella infection. Image obtained from the Public Health Image Library number 4514; Content Provider is the Center for Disease Control and Prevention

Fetuses infected with rubella are at risk for involvement of multiple organ systems. The most common manifestation of congenital rubella syndrome is deafness, followed by ophthalmologic defects such as congenital cataracts, glaucoma, retinopathy, and microphthalmia. Congenital heart defects include patent ductus arteriosus, ventricular septal defects, pulmonary valve stenosis, and aortic coarctation. Arrest in brain development results in microcephaly with severe neurodevelopmental consequences. Abnormal bone marrow development can lead to persistence of embryonic and fetal sources for hematopoiesis, including production from the liver, the spleen, and the skin. Hepatosplenomegaly is seen routinely. Some infants are born with a "blueberry muffin" rash that if inspected microscopically would reveal normal elements of hematopoiesis.

Live attenuated rubella virus vaccine is included in nearly every childhood immunization program worldwide, so congenital rubella syndrome is now only rarely seen. In the USA, rubella immunization is routinely administered as part of the combination measles-mumps-rubella or MMR vaccine at 12 months of age with a second dose administered at kindergarten age.

## 2.4 Fifth Disease, Erythema Infectiosum

Of the six originally numbered febrile rash illnesses of childhood, only fifth disease has retained its numerical designation as the more widely used and accepted name. fifth disease is caused by human parvovirus B19. Virus transmission occurs via respiratory droplets. Following a 3- to 5-day incubation period, the patient develops viremia which can be associated with headache, fever, chills, and upper respiratory symptoms. This marks the period of contagion. A few days later, the "slapped cheek" rash of erythema infectiosum appears. Once the rash appears, the child is no longer contagious [▶ Call Out Box 2.7]. The facial rash is character-

**Call Out Box 2.7**
Once the classic "slapped cheek" rash of fifth disease appears, a clinical diagnosis is made easily. Remember that the patient is no longer contagious after the rash appears.

ized by an intense, confluent, erythematous eruption on the cheeks with sparing around the mouth and nasal bridge. One to four days later, a lacy, reticulated rash often occurs on the remainder of the body, with sparing of the palms and soles. This rash may be pruritic (itchy) and tends to wax and wane before fading over the next several weeks. An uncommon but classic rash that may occur during parvovirus B19 infection includes a dramatic violaceous, raised purpuric rash on the hands and feet in "gloves and socks" distribution. Such a rash is highly unusual, but when seen, parvovirus B19 should be entertained as the most likely culprit.

Post-infectious polyarthritis is known to develop in about 10% of individuals following parvovirus B19 infection. This complication is more common in females, especially those who are infected after adolescence. While the polyarthritis is usually transient, it can become quite disabling. In some women, its persistence mirrors the typical course of rheumatoid arthritis.

A primary cellular target of parvovirus B19 is the erythroid precursor. Virus-infected precursors die, leading to a transient arrest in erythropoiesis. This hematologic complication occurs in all individuals who are infected with parvovirus B19, but typically only presents itself clinically in people who started with an abnormally low red blood cell mass in the first place since a minor, transient drop in red blood cell mass is typically very well tolerated in previously healthy individuals. Patients with hemoglobinopathies, especially homozygous sickle cell disease, can develop a transient aplastic crisis since their red blood cell mass starts low and their circulating erythrocytes already have a shortened half-life. Such patients often need to be supported with erythrocyte transfusions until their own erythrocyte production recovers.

**Call Out Box 2.8**
Like the numbered febrile exanthems of childhood, the herpesviruses that infect humans are classified numerically, such as *H*uman *H*erpes *V*irus 6, or HHV6. Their International Committee on Taxonomy of Viruses Designations are shown here, along with their commonly used names and a few specific examples of the classic illnesses they cause.

| ICTV designation | Commonly used names | Most classic infectious illness(es)[a] |
|---|---|---|
| HHV1 | Herpes simplex type I | Cold sores |
| HHV2 | Herpes simplex type II | Genital herpes |
| HHV3 | Varicella zoster virus | Chickenpox, shingles |
| HHV4 | Epstein-Barr virus | Heterophile antibody positive infectious mononucleosis |
| HHV5 | Cytomegalovirus | Heterophile antibody negative infectious mononucleosis |
| HHV6 | Human herpes virus 6 | Roseola |
| HHV7 | Human herpes virus 7 | None known |
| HHV8 | Human herpes virus 8 | Kaposi's sarcoma, primary effusion lymphoma |
| Nonhuman virus | Herpes B | Severe hemorrhagic meningoencephalitis following a monkey bite |

[a]Herpesviruses cause a broad spectrum of disease in healthy and immunocompromised individuals. Examples listed are classic illness manifestations and represent only a small fraction of the broad array of disease caused by some of these viruses

## 2.5 Roseola, Roseola Infantum, Exanthem Subitum, HHV6 Infection

Roseola infantum is caused by human herpesvirus 6 (HHV-6) [▶ Call Out Box 2.8]. Seroprevalence studies have found that by 3 years of age, most children have been infected with HHV-6.The classic presentation for roseola infantum occurs in children prior to age 3 years and includes a high fever for 3–5 days without an obvious source. The fevers are often quite high, exceeding 40 °C, yet the infant or child does not typically appear ill. HHV6 infection can also lead to a bulging fontanel, and in the presence of the high fever without an obvious source, meningitis is sometimes appropriately ruled out by performing a lumbar puncture. The cause of the fever finally becomes obvious when the rash erupts, which comes at defervescence. The erythematous, maculopapular rash first appears on the trunk and then on the extremities and face. On close inspection, there may be faint halos around the macules and papules. Cough, cervical adenopathy, and swollen eyelids or forehead may also be present. Given the rapid rate of change in body temperature that occurs during HHV-6 infection, febrile seizures can be triggered [2].

## 2.6 Hand Foot and Mouth Disease

Hand foot and mouth disease is a classic summertime febrile rash illness seen almost exclusively among children. Several different enteroviruses are associated with hand foot and mouth disease, with a large majority caused by members of the coxsackie A group, especially coxsackievirus type A16 [2].

**Call Out Box 2.9**
An exanthem is a skin rash that accompanies an illness, typically with fever. Think of an enanthem as a rash on the mucous membranes. When inspecting mucous membranes of the mouse, nose, eyes, and anogenital area of a patient with an infectious illness (with or without an exanthem), note the presence of any ulcers or other eruptions. Refer to these lesions as enanthema.

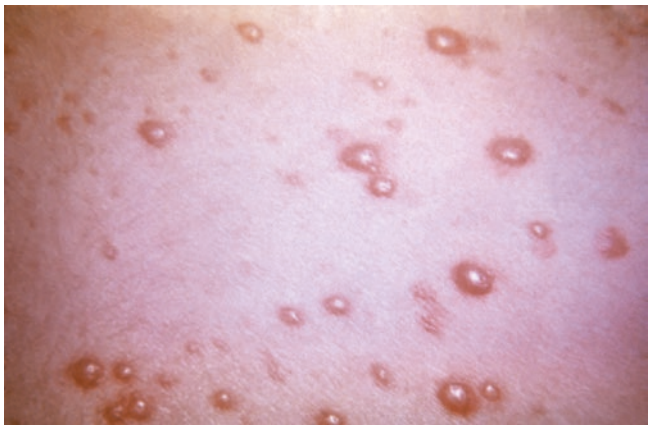
Patients present with malaise and fever, but the most recognizable aspect of the syndrome is the characteristic exanthem on the palms of the hands and the soles of the feet and the characteristic enanthem of the oral mucous membranes (lesions involving the hands, feet, and mouth) [▶ Call Out Box 2.9]. The rash is papular or papulovesicular, and while it is most commonly seen on the hands and feet, more generalized eruptions are not unusual. The enanthem associated with hand, foot, and mouth disease is comprised of painful vesicles and deeper erosions of the oral and oropharyngeal mucosa. When pharyngeal lesions occur without a cutaneous eruption, the illness is referred to as herpangina. Given the vesicular nature of the oral lesions, primary infection with herpes simplex (HSV) type I or II is often included early in the differential diagnosis. The most helpful distinguishing characteristic is that the oral lesions of herpangina are most pronounced posteriorly on the soft palate and pharyngeal wall, while the lesions of primary HSV gingivostomatitis (gingiva, gums; stoma, mouth) are most pronounced anteriorly, often extending beyond the mucous membranes onto the lips. Both illnesses are quite painful. Young children are hesitant to eat or drink and can rapidly become dehydrated.

## 2.7 Varicella, Chickenpox

Chickenpox is the illness that occurs during primary infection with varicella zoster virus. Prior to the widespread use of varicella vaccine in the USA beginning in 1995, varicella infection was universal in children, and its associated rash was easily recognized by most parents and by nearly all health-care providers [7, personal observations]. Since widespread implementation of varicella vaccine, the incidence of varicella has decreased by an estimated 90% [7–9].

Varicella is spread by the airborne route, explaining its very high attack rate when susceptible individuals are exposed. Among unvaccinated cohorts, transmission rates to household contacts exceeds 90%. Secondary cases in the same household are usually more severe than the index case, probably because of the large inoculum of exposure during the prolonged close contact [9]. Immunity, regardless of the severity of the disease or the number of varicella lesions, is usually lifelong.

The incubation period for varicella infection is 10–21 days, with the highest level of contagion occurring 1–2 days prior to the onset of the first pox lesion [9]. The patient is contagious until all the pox lesions have crusted over. Prior to the appearance of the first vesicular "pox" lesion, there is a 1- to 2-day prodrome of fever, malaise, and sore throat. The varicella rash begins as erythematous macules or papules which rapidly progress to clear vesicles on an erythematous base (◘ Fig. 2.4). One classic description for the individual lesions at this stage is the appearance of a "dewdrop on a rose petal" [2]. The vesicles evolve into small pustules, before healing by crusting over. The rash is intensely pruritic. The lesions appear in "crops" so that the patient will have lesions in different stages, from nascent maculopapular lesions to crusted and well-healed lesions at the same time. The rash typically begins on the face or at the scalp line, spreading to the chest and abdomen, and then to the arms and legs. This pattern of eruption is termed "centrifugal" since the rash starts centrally and spreads outwards. The palms and soles are spared [7]. The total number of lesions varies from person to person, averaging 300–400 but often exceeding 1000 [9]. Varicella lesions may also be present on mucous membranes. Enanthema of the oropharynx, tongue, nasal mucosa, urethra, vagina, and anus may also be present.



◘ **Fig. 2.4** The vesicular rash of varicella infection. Image obtained from the Public Health Image Library number 5407; Content Provider is the Center for Disease Control and Prevention

Some individuals previously immunized with varicella vaccine develop varicella infection when exposed; however these "breakthough" cases are typically quite mild, without fever or other systemic symptoms and with fewer than 50 lesions. The lesions of "breakthrough" varicella may not be recognized as varicella infection since they tend to lack the usual vesicular or pustular characteristics [7].

Approximately 1 in every 50 individuals with a classic varicella infection will develop a secondary bacterial skin infection with *Streptococcus pyogenes* or *Staphylococcus aureus.* The pox lesions are intensely itchy. Scratching for relief can unroof the lesions creating breaks in the skin that allow an entry site for the bacterial infection. Some bacterial skin infections are quite severe. The most severe bacterial skin and soft tissue infection, group A streptococcal necrotizing fasciitis, sometimes referred to as "flesh eating strep," is a limb and life-threatening complication of varicella disease. An underrecognized benefit of preventing varicella infection through active immunization programs has been a near elimination of this complication during childhood.

Unlike most other viral exanthems, there are specific therapeutic options for varicella infection that can be considered

depending on the individual circumstances. The antiviral medication acyclovir is effective at blocking replication of the varicella zoster virus and modestly reducing symptoms associated with primary varicella infection. It is most typically used to treat patients with more severe illness and for those at higher risk for developing severe illness.

## 2.8 Exercises

Please refer to the supplementary information section for answers to these exercises.

Match the pathogen with its characteristic skin and or mucous membrane findings.

| Pathogen | Characteristic finding |
|---|---|
| 1. Coxsackievirus A16 | A. Fine papular rash that feels like sandpaper |
| 2. Measles virus | B. Dew drops on rose petals |
| 3. *Streptococcus pyogenes* | C. Dusky red maculopapular rash starting on the race, spreading to the rest of the body |
| 4. *Arcanobacterium haemolyticum* | D. Macular rash that appears when the fevers go away |
| 5. Varicella zoster virus | E. Papulovesicular rash on the hands and feet |
| 6. Rubella virus | F. Slapped cheeks; lacy body rash that waxes and wanes |
| 7. Human herpes virus 6 | G. Looks like scarlet fever, but the tests for *S. pyogenes* are negative |
| 8. Parvovirus B19 | H. A rose-pink macular rash on the face and trunk |

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# Acute and Chronic Lymphadenitis

## Swollen Glands

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**Learning Objectives**

- To review important history and physical examination skills for the assessment of lymphadenitis.
- To understand the diagnostic approach for lymphadenitis and develop a working differential diagnosis of possible etiologies.
- To gain familiarity with the usual treatment regimens for lymphadenitis.



## 3.1 Introduction to the Problem with Definitions

The lymphatic system is an integral part of the immune system consisting of lymphatic organs, lymph nodes, lymphatic vessels, and lymphatic fluid. Lymph nodes are collections of lymphoid tissue interconnected by lymphatic vessels. In the presence of a nearby infection, lymphatic fluid entering a draining lymph node will carry inflammatory debris which may include the pathogen causing the distal infection. In the presence of this inflammatory milieu, the lymph node "reacts." Reactive nodes become enlarged, in part because of the inflammatory process and in part because of intra-nodal lymphocyte proliferation, an important component of a healthy adaptive immune response to infection. A reactive lymph node is enlarged and swollen and may be mildly tender. Lymphatic vessels can also carry viable pathogens from the nearby infection into the lymph node. If pathogen replication exceeds the capacity of the protective host immune response, the lymph node itself becomes infected. When *S. aureus* or *S. pyogenes* are the invading pathogen, the enlarged, swollen lymph node becomes increasingly erythematous, tender, and warm to the touch. This acutely inflamed lymph node is seen clinically as a red, hot, swollen, painful mass referred to as acute bacterial lymphadenitis [▶ Call Out Box 3.1]. Acute bacterial lymphadenitis is common during childhood. The most common anatomic location for the infected lymph node is in the neck, where the anterior cervical lymph node chain receives lymphatic drainage from the mouth and oropharynx. Acute respiratory viral infections are frequently associated with "swollen glands" in the neck as the draining lymph nodes become reactive in response to the infection. In such cases, the enlarged, tender lymph nodes are typically present on both sides and have minimal, if any, associated redness. In contrast, acute bacterial cervical lymphadenitis is unilateral, and the inflamed lymph node(s) is enlarged, tender, red, and warm or hot to the touch.

**Call Out Box 3.1**

The Roman scholar Aulus Cornelius Celsus first described the four cardinal signs of acute inflammation in the first century A.D. as rubor (red), calor (hot), tumor (swollen), and dolor (painful) in *De Medicina*, the only section of a much larger encyclopedic work still in existence.

Cervical lymphadenitis is quite common, but infected lymph nodes can occur in proximity to any distal site that is infected or inoculated with a pathogen. Tracking of an infection along the lymphatic vessel toward the draining lymph node can manifest as acute lymphangitis, appearing as a red, tender linear streak that extends toward the draining lymph nodes. The presence of lymphadenitis, especially when the infection is seen in anatomic locations other than the neck, should trigger a careful history and physical examination for injuries, inoculation sites, or active infections along the anatomic area that is drained by the involved node.

Although often used interchangeably, lymphadenopathy and lymphadenitis describe different pathologies. Lymphadenopathy refers to enlarged lymph nodes. Conditions associated with the presence of "reactive" lymph nodes are therefore associated with lymphadenopathy. Lymphadenitis refers to inflamed lymph nodes. Acute or chronic infection of a lymph node itself elicits a local inflammatory response. As such, infection isolated to a lymph node results in lymphadenitis. Noninfectious triggers of inflammation can also cause lymphadenitis, but such pathology is comparatively uncommon.

## 3.2 Approach to the Medical History

The history of present illness should include the timing of the onset and the duration of the symptoms, the anatomic location affected, and the presence of any associated symptoms. It should be determined whether the patient has had any injuries, breaks in the skin, punctures, bites, or exposure to pets or wild animals. The past medical history should be reviewed to determine whether underlying host factors predispose the patient to infection with specific pathogens. Asking whether any close contacts have been ill may provide additional clues as to the underlying microbiologic cause. Obtaining a travel history helps to identify infections that should be added to the differential diagnosis that might not otherwise be considered.

Understanding the timing of the onset and the duration of the infection is important to differentiate between acute and chronic disease. Subacute lymphadenitis is defined as symptoms lasting between 2 and 6 weeks; chronic lymphadenitis is present when the problem has persisted for longer than 6 weeks. Acute lymphadenitis is typically caused by suppurative (pus-producing) bacteria, whereas chronic lymphadenitis can be caused by a wide range of bacteria, viruses, fungi, and parasites [1] [▶ Call Out Box 3.2].

The anatomic location of infected lymph nodes may also provide clues as to the underlying etiology. Generalized reactive lymphadenopathy, a condition where enlarged, sometimes tender, lymph nodes are present in multiple anatomic locations, occurs during infectious mononucleosis caused by Epstein-Barr virus (EBV) and *Cytomegalovirus* (CMV) and as a finding during acute retroviral syndrome secondary to recent infection with human immunodeficiency virus (HIV). At times, during each of these viral infections, one or more

**Call Out Box 3.2**

| Microbiologic causes of lymphadenitis | | |
|---|---|---|
| Acute bacterial lymphadenitis | | |
| Common | Uncommon | Rare |
| *Staphylococcus aureus* | *Streptococcus agalactiae* | *Pseudomonas aeruginosa* |
| *Streptococcus pyogenes*[a,b] | *Yersinia pestis*[a] | *Serratia* species |
| Oropharyngeal anaerobic flora | *Yersinia enterocolitica*[b] | *Yersinia pseudotuberculosis*[b] |
| | *Francisella tularensis* | |
| Subacute and chronic lymphadenitis | | |
| Common | Uncommon | Rare |
| *Bartonella henselae* | *Mycobacterium tuberculosis*[a,c] | *Cryptococcus neoformans* |
| Nontuberculous mycobacteria | *Actinomyces* species | *Aspergillus* species |
| Epstein-Barr virus[a] | *Histoplasma capsulatum*[a] | *Sporothrix schenckii* |
| *Cytomegalovirus*[a] | *Toxoplasma gondii*[a] | *Candida* species |
| Human immunodeficiency virus[a] | *Brucella* species[a] | *Nocardia* species |

[a]Lymphadenitis often associated with generalized lymphadenopathy
[b]Causes of mesenteric lymphadenitis with pseudoappendicitis
[c]Vaccination with Bacillus Calmette-Guérin (BCG) can result in a chronic suppurative axillary lymph node if inadvertently administered to an immunocompromised patient

lymph node group will appear chronically inflamed. Subacute or chronic cervical lymphadenitis, associated with generalized lymphadenopathy, should raise the possibility that one of these viral infections has trigged the problem. The presence of lymphadenitis in a specific anatomic location other than the neck may alert the astute clinician of a more unusual microbiologic cause. For example, preauricular lymphadenitis is suggestive of adenovirus, *B. henselae*, *or Francisella tularensis* infection while post-auricular lymphadenitis is seen with bacterial or fungal infections of the scalp. At first look, this pattern seems completely random, but it is explained by the different anatomic regions drained by the lymph nodes stationed anteriorly and posteriorly to the ear.

Inoculation or infection of the conjunctivae, which may occur during adenovirus infection, exposure to *B. henselae* after direct contact with a kitten, or exposure to *F. tularensis*, results in lymphatic drainage to the preauricular lymph nodes. The term "Parinaud's oculoglandular syndrome" is used to describe the physical examination findings of preauricular lymphadenitis in the presence of ipsilateral palpebral conjunctivitis. Similarly, the scalp lymphatic vessels drain to the posterior auricular lymph nodes, explaining why infections of the scalp, such as severe tinea capitis, can result in post-auricular lymphadenitis.

Obtaining a detailed exposure history is also important when considering potential causative agents of an infected lymph node. Scratches from a kitten (or less commonly from an adult cat) on the hand or forearm ipsilateral to a subacute or chronically infected epitrochlear (elbow) or axillary lymph node strongly implicate *B. henselae*. *B. henselae* is the primary agent of cat scratch disease. Epitrochlear lymph nodes drain the lymphatic vessels of the hand and ulnar aspect of the forearm, while the axillary lymph nodes drain the thoracic wall, breast, and arm. When lymphangitis appears abruptly on a limb proximal to a cat bite or scratch that occurred within the last 12–24 h, *Pasteurella multocida* is the likely cause, although *S. pyogenes* remains a consideration since both bacterial infections can be rapidly progressive. Cats can also be a source of human infection with *Toxoplasma gondii*, a parasitic cause of subacute and chronic lymphadenitis. Transmission of *T. gondii* results from inadvertent exposure to cat feces, typically during cleaning of the indoor litter box. Like cats, dogs are known to transmit *P. multocida* through bites or other contacts with saliva. *P. multocida* infections are usually abrupt, associated with fever, and progress rapidly with lymphangitic progression from the site of the bite or other exposures within 12–24 h. Patients typically seek medical care and receive antibiotic treatment before the draining lymph node develops the clinical appearance of an acute infection. Nontuberculous mycobacteria cause chronic lymphadenitis, a disease seen almost exclusively in preschool-aged children. Bacteria in this group are ubiquitous in soil. Direct exposure to chickens has also been suggested as a risk factor [2]. Living or working among cattle outside of the USA may result in an exposure to and infection with *Brucella* species, another uncommon cause of chronic lymphadenitis. Glandular tularemia refers to subacute or chronic lymphadenitis caused by *Francisella tularensis*. Exposure typically occurs when an individual is bitten by an infected tick. The bacteria enter the lymphatic vessels draining the area of the tick bite and are carried to the local lymph node(s). If innate host defenses fail to kill the pathogen, the lymph node becomes infected. Individuals who hunt and skin rabbits are at risk for glandular tularemia by directly inoculating *F. tularensis* into breaks in the skin during the handling of the dead animal. In contrast, the act of skinning a rabbit allows for aerosolization and inhalation of the pathogen. This route of exposure results in the development of life-threatening pneumonia with sepsis, rather than chronic lymphadenitis.

In the course of assessing a patient with lymphadenitis, troubling associated signs and symptoms may become evident. Recent unexpected and unexplained weight loss with an associated chronic cough, especially with intermittent hemoptysis, should be assumed to be tuberculosis until proven otherwise. Patients who present with generalized lymphadenopathy associated with weight loss, fatigue, or

pallor should be evaluated for infection with EBV, CMV, and HIV, while other serious noninfectious causes are also entertained, such as hematologic malignancies and lymphoproliferative disorders.



## 3.3 Approach to the Physical Examination

Abnormal findings during a careful, comprehensive physical examination are often essential to uncovering a definitive diagnosis. Inspection of the lymph node(s) identified by the patient as part of their chief complaint is essential. The assessment should include an inspection of the overlying skin and the determination of number, size, shape, texture, mobility, and anatomic location(s) of the affected lymph nodes. The presence of a single inflamed lymph node suggests a localized bacterial infection. The presence of inflamed lymph nodes on both sides of a single anatomic location (e.g., bilateral cervical lymphadenopathy or, less commonly, lymphadenitis) suggests a viral infection. Generalized lymph node involvement indicates a systemic process and expands the differential diagnosis to include a variety of noninfectious possibilities. The size of the lymph node(s) is also important. Cervical lymph nodes are considered enlarged when exceeding 10 millimeters in diameter [1], while inguinal lymph nodes are considered enlarged when measuring more than 15 millimeters in diameter [3]. Normal, healthy lymph nodes are easy to find during a routine physical examination, especially in children. When encountered, they are small, nontender, rubbery in texture, and easily moved around under the skin surface during palpation. Reactive lymph nodes are larger, sometimes modestly tender, rubbery but with a denser texture than nonreactive, normal lymph nodes, and easily mobile under the surface of the skin. Lymph nodes that are acutely infected with *S. aureus* or *S. pyogenes* are enlarged, firm, exquisitely tender, and warm to the touch. The overlying skin may also be acutely inflamed with associated redness, warmth swelling, and tenderness. The characteristics of the involved lymph node(s) and surrounding tissue can change over time to become an inflamed fluctuant mass as an abscess is formed. Physical examination findings of chronic lymphadenitis lack the "angry" features of acute inflammation but are typically bothersome to the patient nonetheless. Redness or violaceous discoloration of the skin may be appreciated. The affected lymph node(s) are enlarged and may be modestly tender. In comparison, enlarged lymph nodes that are hard and fixed suggest the presence of a malignancy. The observed findings of the involved lymph nodes are very helpful in the development of the differential diagnosis but do not obviate the need to complete the physical examination. The presence of abnormal lymph nodes in one location demands a full body lymph node survey to ascertain whether the abnormal lymph node exists in isolation. Other physical examination finders should be noted, as they may indicate important clues about the patient's diagnosis.

The location of lymphadenitis also provides a clue as to the underlying etiology of the infection based on the types of problems typically affecting the anatomical area draining lymph fluid to that lymph node. The scalp should be inspected carefully if posterior occipital or posterior auricular lymph nodes are inflamed. Cervical lymphadenitis is more common in children than in adults because of the higher rates of upper respiratory viral and bacterial infections in this age group. Chronic cervical lymphadenitis in a patient with poor dental hygiene or a history of recent dental surgery should heighten the suspicion for anaerobic bacterial infection, particularly from *Actinomyces* species. The lymphadenitis seen with chronic cervicofacial actinomycosis is also known as "lumpy jaw." The infected lymph nodes can feel quite hard on palpation and are not typically freely mobile suggesting the possibility of a malignancy, such as lymphoma. Lymphatic actinomycosis can also occur in the abdomen following surgery or penetrating trauma.

**Call Out Box 3.3**
Mesenteric lymphadenitis is typically identified during a computed tomography scan of the abdomen and pelvis performed during an evaluation for possible acute appendicitis or other causes of moderate to severe abdominal pain. *Yersinia enterocolitica* and *Y. pseudotuberculosis* are the classically described causes of pseudoappendicitis; however, children with group A streptococcal pharyngitis can also develop impressive mesenteric adenitis with abdominal pain.

The physical examination does not allow for direct visualization of deep thoracic or abdominal lymph nodes. Identification of other less specific abnormalities during the cardiopulmonary or abdominal exam may trigger a request for imaging studies that ultimately reveal pathologic mediastinal, intraperitoneal, mesenteric, or retroperitoneal lymphadenopathy or lymphadenitis [▶ Call Out Box 3.3]. Splenomegaly, with or without hepatomegaly, is a nonspecific finding on the abdominal examination since it can be present during many systemic infections. Lymphadenitis in association with splenomegaly most strongly suggests EBV, CMV, or acute HIV infection.

In addition to examining the skin overlying the infected lymph node, a survey should be performed in search of evidence of an entry site for the infection. Breaks in the skin or any healing evidence of any cuts, scrapes, puncture wounds, or bite marks should be noted. Pointing out their presence to the patient may trigger an important memory of a prior event that was responsible for the exposure that led to the infection.

## 3.4 Diagnostic Testing Used to Evaluate Inflamed Lymph Nodes

Laboratory testing is not always necessary during the evaluation of a patient with suspected lymphadenitis. The presence of history and physical examination findings that are consistent with mild to moderate acute bacterial lymphadenitis in an immunocompetent host with no history of an unusual exposure can be presumed to be infected with *S. aureus* or *S. pyogenes*. Empiric treatment can be prescribed with close

follow-up to be sure the patient improves as expected. A throat culture for *S. pyogenes* should be collected prior to the first dose of antibiotics. Patients who fail to improve during empiric antibiotic therapy should be reassessed. While it's tempting to assume that the failure to improve indicated a flawed empiric diagnosis, the usual explanation is that the infection has organized into an abscess in need of surgical drainage. Incision and drainage removes infected material that is under pressure thereby providing some immediate pain relief. The infected material (all of it, not just a swab) should be sent to the microbiology laboratory for testing. In the vast majority of cases, a Gram stain and bacterial culture of the infected material will provide the definitive diagnosis.

In contrast, more extensive diagnostic testing is typically performed during the evaluation of subacute and chronic lymphadenitis. To begin, nearly every evaluation includes a complete blood count (CBC) and one or more blood biomarkers, which are used to gauge the presence and intensity of acute inflammation (erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and/or procalcitonin). Additionally, necessary diagnostic tests are dictated by clues provided from the medical history or physical examination findings. A list of the most commonly performed tests is found in [► Call Out Box 3.4].

A tuberculin skin test, using purified protein derivative (PPD), should be placed if tuberculosis is suspected. Positive results implicate *M. tuberculosis* infection, but the skin test can also be positive secondary to exposure to, or infection with, nontuberculous mycobacteria and in prior recipients of the Bacillus Calmette-Guérin (BCG) vaccine. Diagnostic testing to evaluate for a patient for suspected tuberculosis can also be done using a blood bioassay. Here, the patient's lymphocytes are exposed to antigens specific to *M. tuberculosis*. If the patient has had prior exposure to or infection with *M. tuberculosis*, the lymphocytes become activated and release interferon gamma. As such, interferon gamma release assays (IGRAs) are more specific than the tuberculin skin test for the diagnosis of *M. tuberculosis* exposure or infection. In most patients, skin testing using a PPD and blood testing using an IGRA are considered equally sensitive for detecting tuberculosis. An important exception is very young children, where the sensitivity of skin testing may be higher than an IGRA.

A chest radiograph is also indicated during the evaluation of subacute and chronic lymphadenitis to determine whether enlarged intrathoracic lymph nodes are also present and to evaluate for lung infiltrates and other findings suggestive of pulmonary tuberculosis or other types of pneumonia that can be associated with lymphadenitis or lymphadenopathy such as histoplasmosis.

Findings from chest radiography, tuberculin skin testing, IGRAs, and pathogen-specific serologies all offer indirect and/or nonspecific etiologic evidence for the underlying cause of an inflamed lymph node. Direct evidence comes from the lymph node itself. Material obtained during needle aspiration [4, 5], incision and drainage, [6] or excisional biopsy [7] should be sent to both the microbiology and anatomic pathology laboratories. Surgically obtained samples should be evaluated in a comprehensive fashion when sufficient sample is available to avoid the need for a repeat procedure simply because a specific test was omitted during the first evaluation. Diagnostic studies typically requested from the microbiology and anatomic pathology laboratories are found in ► Call Out Box 3.5.

### Call Out Box 3.4

**Indirect diagnostic tests performed during an evaluation for subacute and chronic lymphadenitis**

General tests

- Complete blood count and differential
- Erythrocyte sedimentation rate
- C-reactive protein
- Procalcitonin
- Chest radiograph

Serologic tests

- *Bartonella henselae* IgM and IgG
- *Francisella tularensis* IgG
- Epstein-Barr virus IgM and IgG
- *Cytomegalovirus* IgM and IgG
- *Toxoplasma gondii* IgM and IgG
- *Histoplasma capsulatum* IgM and IgG

Other tests

- Skin test: purified protein derivative (PPD)
- Whole blood: interferon gamma release assay for *M. tuberculosis*

### Call Out Box 3.5

**Direct diagnostic tests performed on surgically obtained lymph node material**

| Microbiology laboratory | Anatomic pathology laboratory | |
|---|---|---|
| | *If no solid biopsy tissue is available* | *If solid biopsy tissue is available* |
| Gram stain | Consult with pathologist about the nature of the sample received | Stain for bacteria |
| Bacterial cultures, aerobic and anaerobic | Cytology, if possible | Stain for acid fast bacteria |
| Acid fast stain | Gram stain | Stain for fungi |
| Mycobacterial cultures | KOH stain | Histologic description |
| KOH stain | Acid fast stain | Cell immunophenotyping by flow cytometry, as needed for suspected malignancy |
| Fungal culture | | |

## 3.5 Diagnostic Imaging in the Evaluation of Lymphadenitis

Imaging studies are usually unnecessary for the initial evaluation of acute bacterial lymphadenitis. Ultrasonography can be helpful to determine whether an abscess has formed or to localize an abscessed fluid collection in preparation for needle aspiration or incision and drainage [8]. Computed tomography and magnetic resonance imaging modalities are reserved for the evaluation of anatomy when inflamed lymph nodes are suspected to be compressing or obstructing surrounding structures or during a comprehensive diagnostic evaluation for systemic infectious and noninfectious diseases [1].

### 3.5.1 General Treatment Considerations

Acute respiratory infections quite often cause reactive cervical lymphadenopathy. Viral infections account for the vast majority of these infections, so treatment with antibiotics is usually unnecessary. Of the long list of respiratory viral infections associated with "swollen glands," antiviral therapy is only available for influenza. A common bacterial infection to cause reactive cervical lymphadenopathy is group A streptococcal pharyngitis, or "strep throat." The infection is caused by *S. pyogenes* and requires antibiotic treatment for the pharyngeal infection even in the absence of acute cervical lymphadenitis. Unlike patients who present with reactive lymphadenopathy, those who present with signs and symptoms of acute bacterial lymphadenitis should be treated with antibiotics. In circumstances where surgical intervention is considered, a brief delay in starting antibiotic therapy is appropriate so that cultures can be obtained prior to treatment unless the patient appears toxic. Patients with persistent or worsening symptoms during or following a course of empiric antibiotic therapy targeting *S. aureus* and *S. pyogenes* should be reevaluated as surgical intervention may be required to control the infection [9, 10]. Factors known to increase the need for surgical drainage include younger age, multiple prior visits for medical attention, and the presence of fluctuance at the site of the infected lymph node [11].

### 3.5.2 Specific Treatment Considerations

#### 3.5.2.1 Acute Bacterial Lymphadenitis

Approximately 90% of acute bacterial lymphadenitis cases are caused by *S. aureus* and *S. pyogenes* [12]. Among neonates, *Streptococcus agalactiae* (group B streptococcus) is occasionally identified. A recent history consistent with an upper respiratory tract infection, impetigo, or acute otitis media is present in the majority of cases [13]. Empiric treatment with an antibiotic that targets *S. aureus* and *S. pyogenes*, such as cephalexin (first-generation cephalosporin), is appropriate unless there is a high suspicion for methicillin-resistant *S. aureus* (MRSA) [14]. In such cases, clindamycin is preferred, being mindful that a small percentage of both *S. aureus* and *S. pyogenes* are known to be resistant. Suspected MRSA lymphadenitis can also be targeted empirically with trimethoprim-sulfamethoxazole (TMP/SMX) with the understanding that resistance is becoming more widespread. Moreover, TMP/SMX is not an effective treatment option for *S. pyogenes.* Lack of improvement despite antibiotic therapy indicates that a drainage procedure is needed to achieve resolution. When incision and drainage is performed after several days of antibiotic therapy, the infected fluid may not yield a positive culture, but the procedure is therapeutic nevertheless. Positive culture results help to guide further antibiotic treatment since antimicrobial susceptibility data will be available. On occasion an unexpected pathogen is identified in culture that requires a different therapeutic approach.

Acute bacterial lymphadenitis caused by Gram-negative bacilli, such as *Pseudomonas aeruginosa* and *Serratia* species, is a very unusual finding and should immediately be recognized as such. As appropriate antibiotic therapy is started, testing for an underlying immunodeficiency should begin. Patients with chronic granulomatous disease (CGD), for example, are especially prone to both common and unusual bacterial and fungal infections because of a defect in their neutrophil oxidative burst activity. This immunodeficiency should come to mind in any patient found to have lymphadenitis caused by a Gram-negative bacillus or *Aspergillus* species. It's important to note that patients with CGD are also prone to developing infections with *S. aureus*.

#### 3.5.2.2 Cat Scratch Lymphadenitis

Cat scratch lymphadenitis is a subacute or chronic lymph node infection caused by *Bartonella henselae*. As a nickname, cat scratch disease is preferred over "cat scratch fever" since the majority of patients never develop fever. Infection can occur in draining lymph nodes proximal to any inoculation site, but the disease is the most common cause of axillary lymphadenitis and an almost unique cause of epitrochlear lymphadenitis. The presence of Parinaud's oculoglandular syndrome with preauricular lymphadenitis and associated granulomatous conjunctivitis should always raise the possibility of *B. henselae* infection. Involved lymph nodes are enlarged and firm, typically with minimal discomfort on palpation [15, 16]. The classic, early presence of an inflamed papule at the site of cat scratches distal to the infected lymph node is easily overlooked by the patient and has usually disappeared by the time the inflamed lymph node appears. Cat scratch lymphadenitis is self-limited and does not require antibiotic therapy. Complete resolution may require 6 months or longer. Patients may opt for surgical excision of the enlarged lymph node(s) especially when their location and size result in discomfort. Excisional biopsy is also performed when the diagnosis is uncertain since the signs and symptoms overlap with noninfectious illnesses such as lymphoma. Systemic complications of cat scratch disease are uncommon but can include meningoencephalitis and hepatitis. Even with such dramatic manifestations, the benefit of antibiotic treatment is

controversial [16]. Immunocompromised patients who develop *B. henselae* infections, including lymphadenitis, typically require prolonged parenteral antibiotic therapy [17]. Successful treatment using a single antimicrobial agent has been reported with azithromycin, clarithromycin, ciprofloxacin, trimethoprim-sulfamethoxazole, doxycycline, and rifampin. The optimal choice and necessary duration of treatment are unknown.

#### 3.5.2.3 Actinomycosis

Lymphadenitis secondary to infection with anaerobic bacteria from the genus *Actinomyces* is uncommon. A typical case presents as chronic cervicofacial lymphadenitis in a setting of poor dental hygiene or after dental trauma or oral surgery. *Actinomyces* species are part of the normal microbiome of the human oral cavity and colon [18]. Infected lymph nodes in the craniofacial and cervical regions are called "lumpy jaw" because of their typical woody texture. Since fever is usually low grade or absent [19], a malignancy such as lymphoma is often considered the most likely diagnosis, and a surgical referral for biopsy is made. The collection, transport, and processing of lymph node material destined for tests of malignancy, performed in the anatomic pathology laboratory, include placing the surgical sample in a fixative such as formalin. Tissue fixation is crucial to maintain cellular architecture during histologic evaluation and other tests for malignancy, but the process kills any bacteria that might be present. Since a surgical sample is ideally collected only once, it's important that the surgical team considers sending a portion of the tissue to the laboratory unfixed so that cultures can be performed. Since the clinical findings for some infections and some malignancies overlap, a wise approach taken by many surgeons is to "culture all suspected tumors and biopsy all suspected infections" [▶ Call Out Box 3.6]. The most common anatomic sites for lymphatic actinomycosis include the submandibular and anterior cervical lymph nodes. As the infection begins, evidence of overlying cellulitis may appear. Abscess formation is not unusual. Draining sinus tracks may appear along sites of spontaneous drainage to the skin surface or at the anatomic sites of manipulation during needle aspiration or biopsy [17]. Local spread of the infection beyond the lymph node should be expected without treatment. The infection does not respect tissue planes and has a propensity to extend into the adjacent bone. Lymph node biopsy or fine needle aspiration is used to obtain samples for diagnosis. Microscopically, the surgical specimen will reveal long, Gram-positive, filamentous rods and the presence of sulfur granules [19]. The most common pathogenic *Actinomyces* species are strict anaerobes, so maintaining anaerobic conditions during the collection, processing, and culturing of lymph nodes suspected to harbor the organism is important if culture efforts are to be successful. Even when an excisional biopsy is performed, antibiotic treatment with penicillin or clindamycin is typically recommended for several months [17].

**Call Out Box 3.6**
"Culture all suspected tumors and biopsy all suspected infections"

#### 3.5.2.4 *Mycobacterium tuberculosis* as a Lymph Node Infection

The vast majority of individuals with tuberculosis (TB) have a pulmonary infection. The second most common manifestation of TB is chronic lymphadenitis, a condition also referred to as scrofula. The incidence of scrofula in the USA is low, but the diagnosis should be considered in patients with chronic lymphadenitis, especially those who are high risk because of a known exposure or the presence of an immunocompromising condition [20]. Anatomically, scrofula is most common along the lymph node chain along one side of the neck. Like other infectious causes of chronic lymphadenitis, TB-infected lymph nodes are firm but mobile and minimally tender. The overlying skin may become reddish brown or violaceous but lacks the warmth and bright red color change seen in acute lymphadenitis. As the infection progresses, the lymph nodes undergo caseous necrosis with abscess development with or without draining sinus tracts to the surface of the skin [17]. When the diagnosis is suspected because of the presence of known risk factors, or based on a level of suspicion because of findings on physical examination, several diagnostic tests should be considered. A tuberculin skin test should be placed, or an interferon gamma release assay requested. A chest radiograph should be done to evaluate the patient for the presence of pulmonary TB. Incision and drainage should be avoided because of the increased risk for the development of chronic draining sinus tracts. Any material obtained from the lymph node should be sent to the microbiology laboratory where an acid fast stain can be performed and appropriate cultures initiated. Direct polymerase chain reaction can be used to detect the presence of *M. tuberculosis*-specific DNA. Antibiotic resistance to one or more agents commonly used to treat TB infection is widespread, and while non-culture-based methods are starting to be used to identify isolates with resistance to some of the antibiotics, a cultured isolate is still needed to perform more comprehensive susceptibility testing. Initial treatment of TB lymphadenitis includes four medications. The most common initial regimen includes rifampin, isoniazid, pyrazinamide, and ethambutol (RIPE therapy). Results of antimicrobial susceptibility testing are used to guide the treatment plan. Definitive cure depends on strict adherence to the prescribed regimen of two or more medications for at least 6 months [20].

#### 3.5.2.5 Nontuberculous Mycobacteria (NTM) Lymphadenitis

Nontuberculous mycobacteria (NTM) can infect both immunocompetent and immunocompromised patients alike. Immunocompetent children, typically toddlers and preschoolers, who develop NTM lymphadenitis present with minimally symptomatic unilateral submandibular or cervical lymph node swelling, frequently affecting the region of the

parotid gland [17, 21]. As the infection progresses, the overlying and surrounding skin may become reddish brown or violaceous in color. The involved lymph nodes develop a firm texture. Draining sinus tracts may develop as described for TB infection, especially if an incision and drainage procedure is performed. Clinically, NTM lymphadenitis is indistinguishable from TB lymphadenitis. Because of the presence of cross-reacting antigens in the tuberculin skin test purified protein derivative (PPD), a NTM infection can yield a positive skin test result. Interferon gamma release assays have higher specificity for TB infection than the tuberculin skin test, but their sensitivity in very young children may be suboptimal. A definitive diagnosis of NTM lymphadenitis, therefore, depends on lymph node sampling for acid fast bacterial culture and/or PCR assays. The infection itself is often self-limited in immunocompetent children, but spontaneous resolution can take 6 months or longer. If the infected lymph node(s) are amenable to complete surgical excision, the procedure is curative. Antibiotics have little or no effect on the natural course of the infection, even when the NTM isolate undergoes susceptibility testing in an attempt to guide therapeutic decisions. Immunocompromised patients with NTM lymphadenitis benefit most from surgical removal of the infected material followed by susceptibility-directed antibiotic therapy using a combination of three or more medications. Antibiotic combinations commonly used for the treatment of TB are not effective for the treatment of NTM infections because most other mycobacterial species are resistant to them. Some of the medications and medication classes that have proven useful for in various combinations for the treatment of NTM lymphadenitis in immunocompromised patients include intravenous imipenem/cilastatin, intravenous amikacin, minocycline and other tetracycline derivatives, rifabutin and other rifamycin class antibiotics, levofloxacin and other fluoroquinolone class antibiotics, clarithromycin or azithromycin, and clofazimine [21, 22].

#### 3.5.2.6 *Nocardia* Species Lymphadenitis

Lymphadenitis caused by *Nocardia* species is rare and, when it does occur, is almost always seen in immunocompromised patients. The clinical presentation is similar to that seen with other causes of chronic lymphadenitis. The diagnosis is made when the clinical microbiology laboratory recovers the organism from lymph node biopsy material that was submitted for culture [17]. *Nocardia* species infections are treated with antibiotics in combination with surgical removal when feasible. The necessary length of antibiotic therapy is measured in months and depends on the severity of the infection, the extent to which the infected material has been removed surgically, and the degree of immunocompromise of the patient. Trimethoprim-sulfamethoxazole remains the drug of choice for most *Nocardia* species infections, although many isolates are also highly susceptible to penicillins, clindamycin, and linezolid.

### 3.5.3 Viral Causes of Generalized Lymphadenopathy

#### 3.5.3.1 Infectious Mononucleosis: Epstein–Barr Virus and *Cytomegalovirus*

Infectious mononucleosis is an illness most commonly seen among adolescents and younger adults. Patients present with fever, exudative pharyngitis with tonsillar hypertrophy, splenomegaly, fatigue, and generalized lymphadenopathy. Enlarged lymph nodes are most evident in the neck, axillae, and groin. One or more of the enlarged lymph nodes may persist, and mild to moderate discomfort associated with their presence mirrors the signs and symptoms of chronic lymphadenitis. Epstein-Barr virus is the most common cause of infectious mononucleosis. *Cytomegalovirus* (CMV) accounts for most of the remaining cases. A complete blood count performed during the acute phase of the illness usually shows an elevated percentage of circulating atypical lymphocytes. The detection of serum heterophile antibodies (a positive "monospot" test) supports the clinical suspicion of EBV infection, but a definitive diagnosis requires serologic testing for the detection of immunoglobulin M (IgM) directed against EBV viral capsid antigen [23]. Acute CMV infection is diagnosed by detecting serum anti-CMV IgM. Treatment for infectious mononucleosis is supportive, with no role for the routine use of antiviral medications or systemic glucocorticoids [24].

#### 3.5.3.2 Acute Infection with Human Immunodeficiency Virus

Recent infection with human immunodeficiency virus (HIV) is associated with an infectious mononucleosis-like illness referred to as acute retroviral syndrome. Between 2 and 4 weeks after HIV exposure, individuals who develop primary infection experience fever, fatigue, and generalized lymphadenopathy [25]. The systemic symptoms may last several weeks to months but eventually subside leaving long-term generalized or regional lymphadenopathy. Mild to moderate discomfort associated with the presence of the swollen lymph nodes mirrors the signs and symptoms of chronic lymphadenitis. HIV infection is diagnosed through the detection of circulating HIV-specific antibodies and/or HIV-specific antigen. Treatment relies on highly active antiretroviral therapy (HAART) with a goal to completely suppress virus replication. Effective antiviral therapy can reduce any residual lymphadenopathy. In cases where HAART therapy is delayed and the patient has already developed a serious cellular immunodeficiency secondary to depletion of CD4+ T lymphocytes, antiretroviral therapy can trigger an immune reconstitution syndrome with an associated generalized lymphadenopathy [26].

### 3.5.4 Fungal Causes of Lymphadenitis

► Call Out Box 3.2 includes several possible fungal causes of subacute or chronic lymphadenitis. Most are quite rare and will not be discussed further, but infections caused by *Histoplasma capsulatum* are seen regularly enough to warrant a brief description.

*H. capsulatum* is one of several dimorphic fungi that can cause chronic lymphadenitis. Infections are usually localized to the lungs, but lymph node infections do occur with or without a primary lung focus. In the USA, histoplasmosis is seen most commonly among individuals who live in or around the Mississippi, Ohio, and Missouri river valleys. Immunocompromised individuals, young children, and the elderly are at higher risk than others for developing infection. In the presence of risk factors, histoplasmosis can disseminate rapidly causing a life-threatening, systemic infection. Diagnosis requires either growth of the mold from the involved lymph node or other systemic sites, but even without positive cultures, serologic testing and/or urinary antigen testing can provide supportive evidence of infection. In immunocompromised patients, and in individuals suspected to have disease extending beyond a single group of lymph nodes, chest radiograph or computed tomography of the head, neck, and chest is useful. The presence of parenchymal lung disease with mediastinal adenopathy is not unexpected. Antifungal therapy is indicated for acute infection in those at high risk, but immunocompetent patients do not always require treatment since the illness is usually self-limited. When treatment is used for lymphadenitis, itraconazole is preferred unless severe systemic infection is also present. Under such circumstances, amphotericin B is administered until clinical improvement is evident, followed by a prolonged course of treatment with itraconazole [17].

### 3.5.5 Parasitic Causes of Lymphadenitis

#### 3.5.5.1 *Toxoplasma gondii*

Infection with *Toxoplasma gondii* is referred to as toxoplasmosis. The disease is caused by an obligate intracellular protozoan. While most infections are asymptomatic, previously healthy patients who develop symptoms complain most commonly of swollen and tender cervical or occipital lymph nodes that persist for 4–6 weeks. Immunocompetent individuals have a benign illness that mirrors that described for infectious mononucleosis. The chronic lymphadenitis resolves without specific antibiotic treatment [27, 28]. Patients who are pregnant or immunocompromised can develop serious complications. During pregnancy, the parasite can be vertically transmitted to the fetus causing severe congenital defects. Immunocompromised individuals can develop systemic infection with multisystem disease. Whenever treatment is deemed necessary, pyrimethamine and sulfadiazine are used in combination with folinic acid.

## 3.6 Summary

Lymphadenitis is an inflammatory condition of lymph nodes, most often caused by an infection. It can be acute, subacute, or chronic in nature and can be caused by a wide variety of pathogens. A thorough history and physical examination is important as the findings provide hints as to the underlying cause of the infection. Lymphadenitis is more common in children than in adults. The anatomic sites most frequently affected are the lymph node chains in the neck. Diagnostic evaluation may require blood tests, skin testing for TB, imaging, and/or sampling of infected tissue for culture. Antimicrobial therapy is not always needed but, when used, should be directed toward the most likely cause of the infection while the diagnostic evaluation is being completed.

## 3.7 Exercises

Please refer to the supplementary information section for answers to these exercises.

? 1. A previously healthy 3-year-old girl with a 3-day history of sore throat, fever, rhinorrhea, and congestion is found to have an enlarged lymph node in her neck. It is not red, tender, or fluctuant. Physical examination of her ears, nose, and throat is unremarkable. She appears well and is active and playful in the examination room. A point of care test on a throat swab is negative for group A streptococcus. Of the following, the most appropriate course of action is:
   A. Treat the girl with amoxicillin
   B. Provide supportive care
   C. Obtain blood work, including a complete blood count and C-reactive protein
   D. Obtain a computer tomography scan of her head and neck

? 2. Of the following, the most common cause of acute bacterial lymphadenitis is:
   A. *Actinomyces* species
   B. *Bartonella henselae*
   C. *Staphylococcus aureus*
   D. *Mycobacterium tuberculosis*

? 3. A previously healthy 18-year-old female complains of generalized fatigue, fever, sore throat, and swollen, sore glands in her neck of 3 days' duration. On abdominal examination she has mild left upper quadrant tenderness. The spleen is palpable at the costal margin. A throat swab for group A streptococcus, and a blood heterophile antibody test are both negative. Of the following tests, which is most likely to reveal the diagnosis?

A. Tuberculin skin test
B. Epstein-Barr-specific anti-IgM against viral capsid antigen
C. Lymph node biopsy
D. Polymerase chain reaction specific for human immunodeficiency virus

3

4. Of the following, the most common cause of subacute unilateral axillary lymphadenitis is:
A. *Bartonella henselae*
B. *Francisella tularensis*
C. *Staphylococcus aureus*
D. *Streptococcus pyogenes*

5. The four cardinal signs of acute inflammation are:
A. Diarrhea, conjunctivitis, erythroderma, and headache
B. Bleeding, warmth, pain, and rash
C. Blisters, swelling, pain, and stiffness
D. Redness, swelling, heat, and pain

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# Infections of the Respiratory Tract

Contents

# Otitis, Sinusitis, and Mastoiditis

## Ear or Facial Pain Following a Common Cold

*Winter S. Berry*




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**Learning Objectives**

- Know the common clinical presentations for otitis, sinusitis, and mastoiditis.
- Identify common and uncommon microbiologic causes of otitis, sinusitis, and mastoiditis.
- Understand the distinguishing characteristics for acute, recurrent, and chronic clinical courses of each disease.
- List the important risk factors for developing severe infections of the paranasal sinuses.
- Outline the approach to diagnosis, including signs and symptoms that warrant laboratory or imaging evaluations.
- Describe the indications for medical and surgical treatment of otitis, sinusitis, and mastoiditis.

## 4.1 Otitis

### 4.1.1 Introduction

The term "otitis" encompasses pathology of both the middle and outer ear. It is generally divided into two categories – otitis media and otitis externa. Otitis media can present either as an acute infectious process of the middle ear (acute otitis media) or as a serous noninfectious process (otitis media with effusion). Otitis externa is an infectious inflammatory condition of the external auditory canal (EAC). Approaches to the diagnosis and treatment of acute otitis media have evolved over the last several decades as new immunizations, and more antibiotic choices have become available.

## 4.2 Definitions

**Otitis media with effusion (OME)** – A collection of serous fluid in the middle ear space without signs of acute inflammation. OME is not an infectious process.

**Chronic otitis media with effusion (COME)** – A collection of serous fluid in the middle ear space that persists for more than 3 months

**Acute otitis media (AOM)** – An acute infection of the middle ear with signs and symptoms of acute inflammation. An effusion is also present.

**Recurrent AOM** – Three or more episodes of AOM in a 6-month period or 4 or more episodes of AOM in a 12-month period

**Otorrhea** – The presence of a discharge from the ear

**Chronic suppurative otitis media (CSOM)** – The presence of a purulent middle ear effusion associated with otorrhea, secondary to chronic tympanic membrane perforation, for more than 6 weeks in the setting of antibiotic treatment

**Otitis externa (OE)** – An infection of the external auditory canal

## 4.3 Basic Concepts

### 4.3.1 Otitis Externa

Acute otitis externa develops following disruption of the epithelial cell layer of the EAC. Epithelial breakdown can be caused by excessive moisture that leads to maceration, trauma during insertion of a foreign body, occlusion by a device such as a hearing aid or earplug, or dermatologic conditions involving the EAC. Excessive moisture as a cause for breakdown or maceration of the skin that lines the EAC is very common. The frequency of otitis externa among swimmers underscores the importance of keeping the EAC dry and explains why otitis externa is commonly known as "swimmer's ear."

The presenting symptoms of otitis externa include otalgia, decreased hearing, sensation of fullness in the ear canal, pruritus, tenderness on palpation, and movement of the EAC or the pinna. Otorrhea, adjacent cervical lymph node enlargement, and local cellulitis may develop later in the course of more severe cases. The most common bacterial causes of OE include *Pseudomonas aeruginosa* and *Staphylococcus aureus* [1]. Typical physical examination findings include erythema and edema of the EAC with debris, cerumen, and purulent material filling the canal. Visualization of the tympanic membrane (TM) is often obstructed by the otorrhea and the swelling associated with the inflammation. An unimpaired view of a normal TM, with visible landmarks, is shown in Fig. 4.1. The diagnosis of OE is made based on the history and the clinical findings. Typical otoscopic findings of OE are shown in Fig. 4.2. When the EAC is cultured, one must be cognizant that culture results may reflect EAC flora rather than a causative organism. First-line antibiotic treatments include topical otic drops of a fluoroquinolone, such as ciprofloxacin with or without topical glucocorticoid drops. If edema of the EAC is severe, placement of a wick inside the EAC may be necessary to ensure delivery of medication to the more proximal areas of infection. Risk of recurrence of OE is increased in individuals with atopic dermatitis, seborrhea, immune compromise, and repeated local trauma to the area when

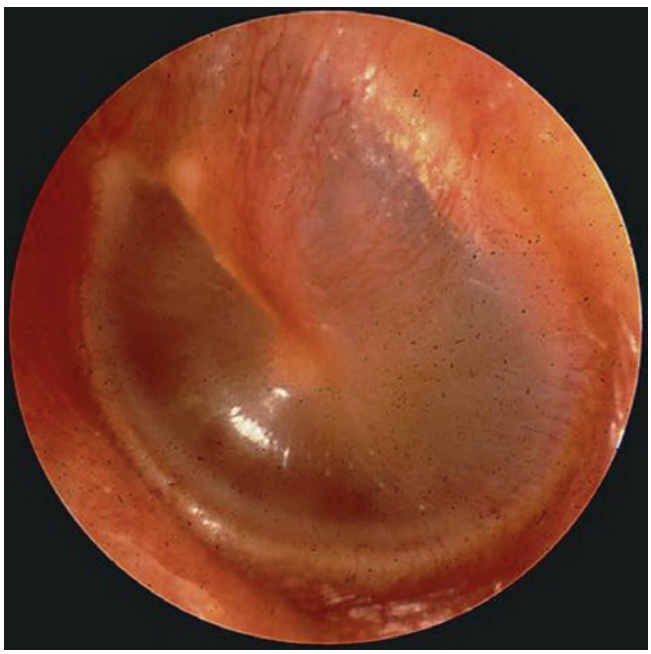

**Fig. 4.1** Normal tympanic membrane. (Courtesy of Dr. Charles Woods, SUNY Upstate Medical University)

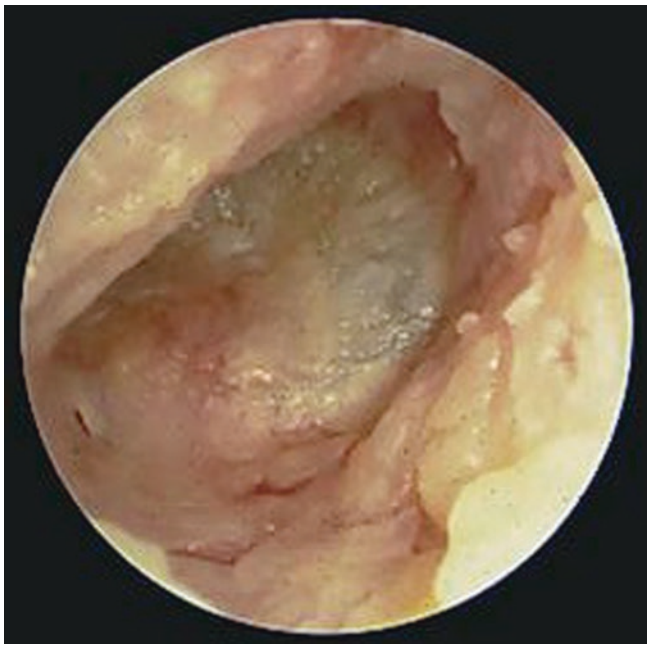

**Fig. 4.2** Otitis externa. (Courtesy of Dr. Charles Woods, SUNY Upstate Medical University)

cleaning the ear. A fungal etiology of the infection should be considered when otorrhea is prolonged, especially if topical antibacterials and a wick have been used already. Individuals who use hearing aids and those who have had recent bacterial infections are also at risk for fungal disease. The most common fungal etiologies include *Aspergillus* and *Candida* species [1].

### 4.3.2 Acute Otitis Media

The development of AOM begins when there is dysfunction of the eustachian tube. Under normal conditions, the eustachian tube allows the middle ear to drain to the pharynx and to equalize pressure between the middle ear and the environment. Impaired drainage may be present for several reasons. The anatomic position of the shorter eustachian tube in young children maintains a relatively horizontal orientation allowing the drainage to defy gravity. Adenoidal hypertrophy and anatomic anomalies of the palate can also block or impair normal drainage. The presence of gastroesophageal reflux disease, allergic rhinitis, and viral upper respiratory infections can all lead to inflammation of the eustachian tube and surrounding tissues resulting in the presence of increased secretions in the middle ear that accumulates because the eustachian tube is not fully patent [2–4]. In each of these clinical scenarios, negative pressure develops in the eustachian tube and middle ear space. The small number of bacteria normally present in those secretions replicates in the now closed space resulting in acute infection (AOM). Retained nasopharyngeal secretions are very common in individuals with otherwise uncomplicated viral respiratory infections. A subgroup of these individuals experience secondary bacterial infection because the initial viral infection and its associated inflammation allow for the closed space conditions where the bacteria can thrive.

### 4.3.3 Risk Factors

The risk factors for AOM include any condition that promotes eustachian tube dysfunction. The relative horizontal position of the eustachian tube during early childhood explains why the peak incidence of AOM is between 6 and 18 months of age. Additional risk factors include children who develop their first episode of AOM prior to 6 months of age, children in daycare, and the presence of atopy, adenoidal hypertrophy, chronic sinusitis, ciliary dysfunction, immune-compromising conditions, and craniofacial anomalies. Individuals with trisomy 21 are especially prone to otitis media because their eustachian tubes are short and their pharyngeal muscle tone is weak [2, 3].

### 4.3.4 Microbiologic Causes of AOM

An accurate description of the infectious etiologies of AOM requires that middle ear fluid is removed during acute infection and submitted for microbiologic testing. The procedure to remove the fluid, tympanocentesis, is no longer performed on a routine basis. Most of the literature that describes the microbiologic causes of AOM was published before the routine introduction of *Haemophilus influenzae* type B (late 1980s) and heptavalent (2000) and 13-valent (2010) conjugate pneumococcal vaccines. Rates of viral, bacterial, and mixed culture results from middle ear effusion vary significantly across those studies with rates of bacterial infection ranging between 50% and 90% of all AOM. The most common viral causes include respiratory syncytial virus; parainfluenza viruses, types 1, 2, and 3; influenza A and B viruses; adenovirus; coronaviruses; parechoviruses; and human metapneumovirus.

The most common bacterial causes of AOM include *Streptococcus pneumoniae*, non-typeable *Haemophilus influenzae*, and *Moraxella catarrhalis*. *S. pneumoniae* was unequivocally the most common bacterial agent of AOM before conjugate pneumococcal vaccine was added to the universal pediatric immunization schedule in 2000. Following vaccine introduction, non-typeable *H. influenzae* became more predominant, and "replacement" pneumococcal serotypes that were not included in the 7- or 13-valent vaccines emerged [2–4].

Non-typeable *H. influenzae* should be suspected in the clinical setting of AOM when purulent conjunctivitis is also present. Suspicion that *H. influenzae* could be the underlying cause of the patient's condition is important, because unlike *S. pneumonia*, *H. influenzae* may produce a beta-lactamase, an enzyme that inactivates some of the most common antibiotics used empirically to treat AOM, such as amoxicillin. Less common bacterial etiologies of AOM include

*Streptococcus pyogenes* (also known as group A streptococcus, the cause of "strep throat") and *Staphylococcus aureus*. *S. pyogenes* is more commonly seen among those older than 5 years of age. Its presentation is typically quite aggressive leading to perforation of the TM and/or accompanying mastoiditis [2]. *S. aureus* should be included on the list of possible infecting agents in patients who have tympanostomy tubes, as these medical devices serve as a conduit between the bacteria normally present in the EAC and the middle ear. *Streptococcus agalactiae* (also known as group B streptococcus) should be considered as a possible causative organism in AOM when the process is identified in neonates and very young infants.

The microbiologic culprits responsible for chronic suppurative otitis media include *S. aureus*, *Pseudomonas aeruginosa*, *and S. pneumonia*. Chronic suppurative otitis media is especially common among individuals from Southeast Asia, the Western Pacific, Africa, and Native Americans of the desert southwest [2].

### 4.3.5 Approach to the Diagnosis of AOM

AOM is a closed space infection. As the infection progresses, symptoms change from a feeling of fullness to general achiness. The pain intensifies as the pressure in the infected space increases until that pressure is relieved. Relief may come spontaneously as serous fluid is reabsorbed or when the pressure exceeds the capacity of the TM and the eardrum ruptures. Tympanocentesis can also be used as a controlled technique to remove middle ear fluid and thereby reduce the pressure. AOM causes ear pain. The pain in young children can manifest itself as fussiness, sleep disruption, or ear tugging. Fever is expected in young children with AOM, but uncommon among older children and adults with AOM. In cases where the TM ruptures, the pain is relieved, but the patient or parent will note a purulent or bloody ear discharge.

A diagnosis of AOM is often suspected while obtaining the history of the illness. The diagnosis is confirmed by finding on the physical examination. A thorough otoscopic exam, including pneumatic otoscopy and clear visualization of the TM and EAC, is essential. Presuming a diagnosis of AOM in the absence of a thorough examination leads to overdiagnosis and subsequent overuse of antibiotics. Pneumatic otoscopy should always be included to assess the mobility of the TM. Efficient pneumatic otoscopy is aided by using a speculum with a tight seal of the EAC [4]. Classic otoscopy findings of AOM include the presence of fluid in middle ear space, outward bulging of the TM secondary to the increased pressure in the middle ear space, loss of visualization of ossicle bony landmarks behind the TM, and erythema or injection of radial vessels on the TM. The middle ear effusion is purulent in AOM but must be carefully distinguished from opaque noninfectious effusions secondary to OME. The absence of erythema of the TM suggests a diagnosis of OME, not AOM. A bulging TM with decreased mobility on pneumatic otoscopy is the most specific exam finding for bacterial AOM [4]. The presence of purulent otorrhea in the EAC is seen if a TM perforation has occurred before the time of examination. This finding must be distinguished from the edema and erythema that occur along the EAC during otitis externa. Bullae may be present on the TM in conjunction with other signs of acute inflammation. The findings are consistent with a form of AOM termed bullous myringitis. The presence of bullae does not suggest a specific microbiologic cause nor does it change the clinical approach to the condition.

In summary, the clinical diagnosis of AOM is made when there is an acute onset of symptoms, the presence of a middle ear effusion, and objective signs of acute middle ear inflammation such as a red bulging eardrum that does not move during pneumatic otoscopy [2–4].

The diagnosis of AOM does not involve any laboratory evaluation or radiographic imaging unless there is evidence for a significant complication or severe or persistent disease. Tympanocentesis with culture of the middle ear effusion is the gold standard for diagnosing the etiologic agent of AOM, but is only necessary in a small subset of cases. When necessary, referral to an otolaryngologist is considered the best practice for those who are not certified and experienced in performing the procedure. The inclination to collect samples from the EAC for microbiologic cultures, even in cases where there is frank otorrhea, is generally discouraged since the laboratory results often reflect EAC flora rather than identifying the true causative organism(s).

### 4.3.6 Differential Diagnosis of AOM

The differential diagnosis for AOM includes otalgia secondary to OME, referred pain from dental or pharyngeal disease, local herpes zoster infection, otitis externa, adjacent soft tissue infection, or eustachian tube dysfunction secondary to alternative causes.

### 4.3.7 Treatment of AOM

Recommendations for the treatment of AOM have evolved over the past several decades. Depending on the details of the clinical circumstance, current recommendations now permit a clinical observation period as an alternative to immediate antibiotic therapy for many cases. This approach is supported by the knowledge that many cases are caused by respiratory viruses and by evidence demonstrating that a reasonable proportion resolve without intervention. Ultimately, the approach used should carefully weigh patient-specific factors such as age, severity of presenting symptoms, risk factors for severe infection, history of AOM, and the patient's availability to follow up. Safety-net antibiotic prescriptions (SNAP) and wait-and-see prescription (WASP) are prescriptions provided at the time of diagnosis allowing patients and families to employ watchful waiting, with the option to fill an antibiotic prescription if the symptoms persist or worsen over the

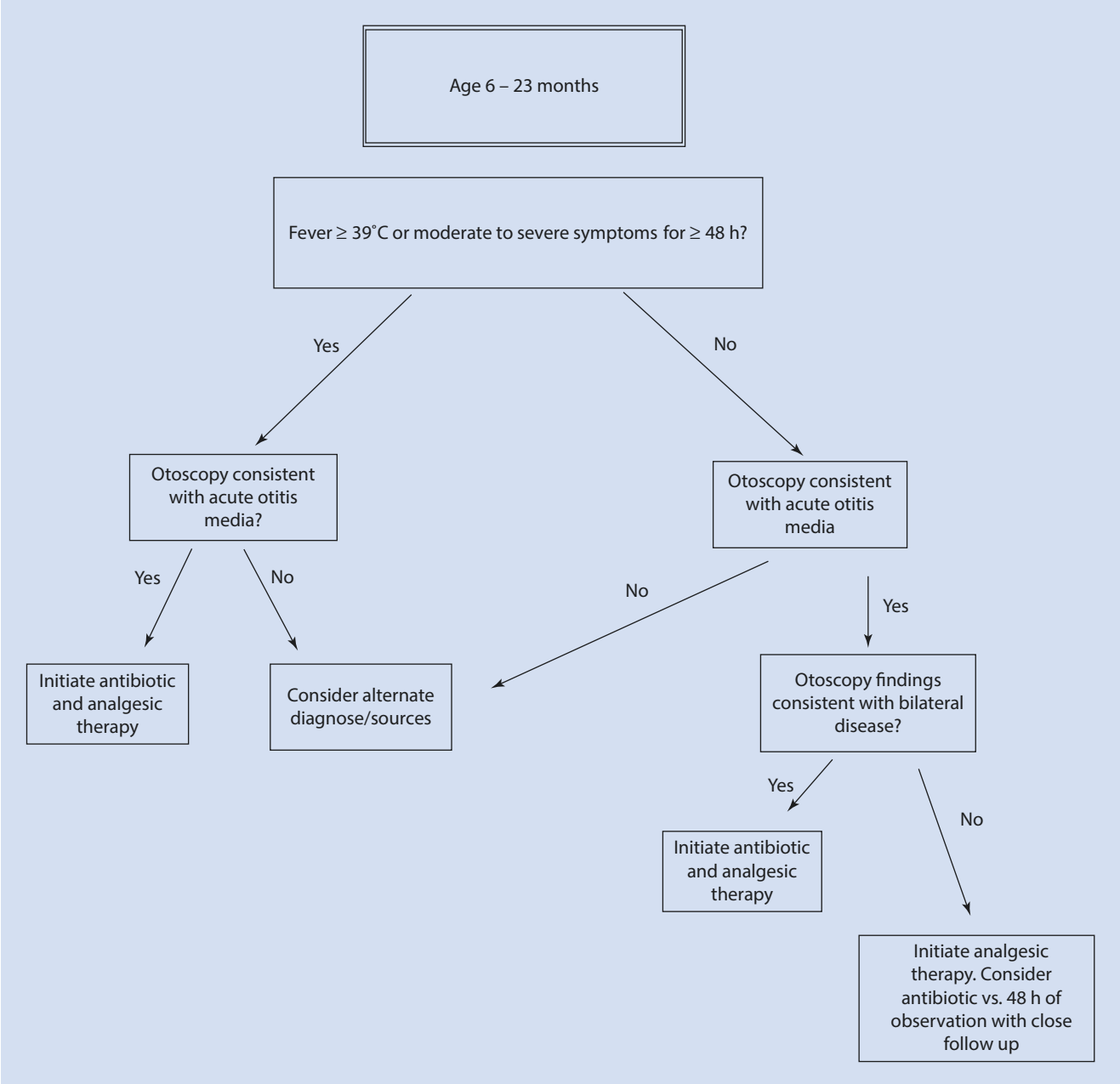


**Fig. 4.3** Treatment of AOM in patients <24 months of age

next 48–72 h [2–4]. Treatment approach algorithms that account for age, examination findings, and illness severity at the time of presentation are shown in Figs. 4.3 and 4.4. Analgesic should be used regularly early in treatment course to provide symptomatic relief of otalgia [2, 4].

The first-line antibiotic choices for the treatment of AOM are shown in ▶ Call Out Box 4.1 [4]. High-dose amoxicillin (80–90 mg/kg/day) is recommended to overcome concerns about adequate coverage against penicillin nonsusceptible *S. pneumonia*. Recommendations regarding duration of antibiotic therapy are age dependent. Except for intramuscular ceftriaxone, a 10-day course is recommended for children less than 2 years of age, whereas a 7-day course can be considered for children between 2 and 5 years of age. A 5- to 7-day course is usually adequate starting at 6 years of age through adulthood [4].

Antibiotic therapy for the treatment of CSOM requires administration of topical fluoroquinolone antibiotic drops with or without glucocorticoid drops. The medications are able to reach the middle ear space by crossing through the perforation in the TM. Fluoroquinolones are used because their spectrum of activity includes the most common etiologic agents including *P. aeruginosa*.

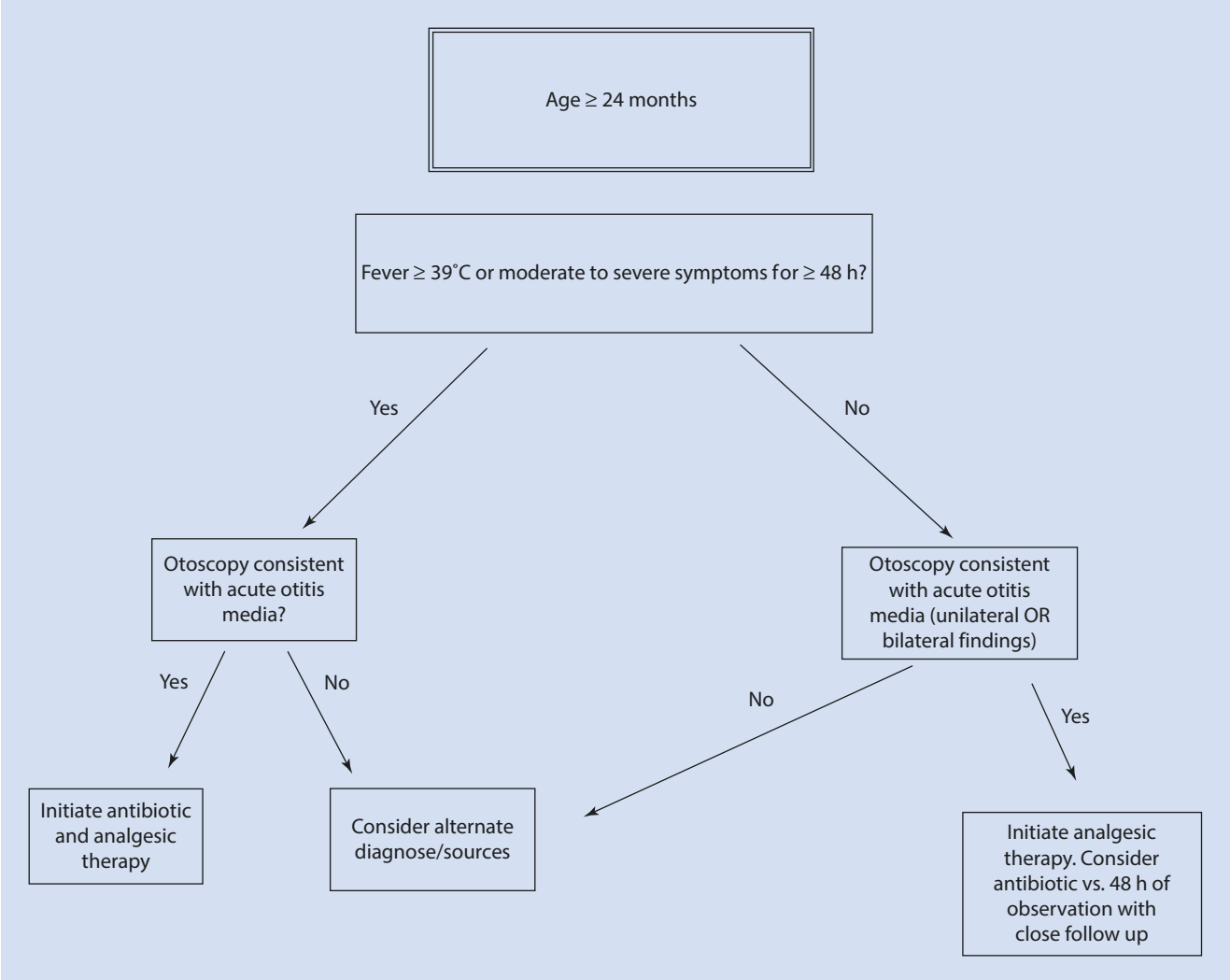


**Fig. 4.4** Treatment of AOM in patients >24 months of age

**Call Out Box 4.1**

**Antibiotic Choices for the Treatment of Acute Otitis Media**

- Uncomplicated AOM: high-dose amoxicillin
- The presence of a type 1 hypersensitivity to penicillin: azithromycin or clarithromycin
- The presence of a non-type 1 hypersensitivity to penicillin: 3rd-generation oral cephalosporin such as cefdinir.
- Previous antibiotic treatment in the past 4 weeks: amoxicillin plus clavulanic acid
- Amoxicillin failure at 48–72 h: amoxicillin plus clavulanic acid
- AOM with purulent conjunctivitis: amoxicillin plus clavulanic acid
- Amoxicillin plus clavulanic acid failure at 48–72 h: 3rd-generation oral cephalosporin such as cefdinir or intramuscular ceftriaxone for 1, 2, or 3 days
- Ongoing emesis or adherence concerns: intramuscular ceftriaxone for 1, 2, or 3 days

### 4.3.8 Complications of AOM

Complications of AOM encompass spread of infection to structures adjacent to the middle ear and include mastoiditis, petrositis, venous sinus thrombosis, and central nervous system infection including brain abscess.

### 4.3.9 Follow–Up

Patients under treatment or observation for AOM should be reevaluated for the persistence or worsening of symptoms 48–72 h after the initial assessment. If symptoms are improving at 48–72 h, short-term follow-up is not usually necessary. TM abnormalities seen on physical examination can persist for up to 12 weeks.

**Case Study**

### Practical Examples

**Case 1**

A 17-month-old girl presents with a 3-day history of rhinorrhea, cough, fussiness, and sleeping less than usual. Her highest recorded temperature over the course of illness is 37.7C. Her mother is concerned that she may have an ear infection. On physical examination she has clear rhinorrhea. Her left TM is unremarkable. The right TM is slightly opaque and has clear fluid behind it. The radial blood vessels of the TM are not injected. On pneumatic otoscopy, the right TM slightly reduced mobility. The heart and lung examinations are normal.

- What is the diagnosis?
- Are antibiotics warranted?

**Discussion**

This common clinical scenario offers a description of otitis media with effusion (OME). While the history of present illness includes upper respiratory infection symptoms and fussiness (a possible sign of ear pain in a toddler), and acute otitis media (AOM) is common in this age group, her physical examination findings are not consistent with AOM. The presence of a simple effusion in the middle ear space, in the absence of other signs of TM inflammation, is likely due to poor drainage of the eustachian tube in the setting of her current viral illness. She does not meet criteria for a diagnosis of AOM. Antibiotics are not warranted since the middle ear effusion is very unlikely to be due to a bacterial infection.

**Case 2**

A 4-year-old boy presents with a complaint that "my ear hurts!." His illness started with a cough and rhinorrhea 10 days earlier. He first developed fever 2 days ago. Despite this illness, the child has been able to participate in most of his usual activities. He has history of AOM with his last episode diagnosed 9 months ago. He has not taken antibiotics for any other reason since then. He has no medication allergies. On examination, the boy has clear rhinorrhea, mild pharyngeal injection, clear conjunctivae, and normal heart and lungs. His right external auditory canal is unremarkable. The right tympanic membrane shows intact bony landmarks and a small meniscus of clear effusion in the middle ear space. The left external auditory canal is unremarkable. His left TM is bulging and erythematous with a loss of the usual bony landmarks. The radial blood vessels are bright red. There is absence of mobility on pneumatic otoscopy.

- What is the child's diagnosis?
- What is the correct treatment approach?
- If antibiotics are prescribed, what would be the first-line treatment option?

**Discussion**

The child's clinical history of otalgia with fever, preceded by an upper respiratory infection, along with physical examination findings of middle ear inflammation is consistent with left-sided acute otitis media. While the diagnosis is clear, the recommended approach to treatment offers two options. The boy is older than 24 months of age, his otalgia is not severe, and his fevers are under 39 °C. Under these circumstances, it is appropriate either to initiate antibiotic therapy *or* to wait and observe to determine whether his symptoms resolve on their own. Symptoms that persist or worsen during observation warrant the initiation of antibiotic therapy. The patient or the family may be given a "wait-and-see" prescription in this instance with instructions to fill it only if the symptoms do not improve in 48–72 h. The boy in the vignette should be treated as a case of uncomplicated AOM without recent antibiotic exposure. Since he has no medication allergies, high-dose amoxicillin (80–90 mg/kg/day) is the antibiotic treatment of choice.

## 4.4 Sinusitis

### 4.4.1 Introduction

Sinusitis refers to an infection of one or more of the paranasal sinus cavities. Acute upper respiratory viral infections that cause the common cold all involve the paranasal sinuses. The vast majority of these infections are self-limiting and do not require treatment with antibiotics. Acute bacterial rhinosinusitis is a more precise name for the condition caused by bacterial pathogens, and like AOM, it typically occurs when drainage is impaired secondary to the inflammation associated with a recent viral infection. Fortunately, only a small number of "colds" become complicated by acute bacterial sinusitis. While viruses and bacteria account for most infections of the paranasal sinuses, molds can cause some of the more severe disease. Immune-compromised patients are particularly vulnerable to these disfiguring, often fatal mold infections.

## 4.5 Definitions

### 4.5.1 Sinusitis: Inflammation of the Paranasal Sinus Cavity Mucosa

**Acute bacterial rhinosinusitis (ABRS)** – A bacterial infection leading to inflammation of the paranasal sinuses which resolves, with treatment, within 30 days

**Subacute bacterial rhinosinusitis (SBRS)** – A bacterial infection leading to inflammation of the paranasal sinuses which resolves in 30–90 days

**Recurrent acute bacterial rhinosinusitis (RABR)** – Bacterial infections leading to inflammation of the paranasal sinuses lasting fewer than 30 days but recurring 3 or more times in a 6-month period *or* 4 or more times during a 12-month period. Each infection responds well to treatment with antibiotics, and the patient experiences at least 10 symptom-free days in between episodes.

**Chronic sinusitis** – Inflammation of the paranasal sinuses for more than 90 days with persistent symptoms. This condition is most commonly associated with noninfectious processes such as environmental

allergies, reactions to environmental pollutants, and gastroesophageal reflux disease. Patients with cystic fibrosis and ciliary dyskinesia are especially prone to chronic sinusitis secondary to noninfectious and infectious triggers.

## 4.6 Basic Concepts

### 4.6.1 Anatomy and Pathophysiology

The anatomy of the paranasal sinuses changes from birth, not becoming fully aerated until adulthood [5, 6]. The ethmoid sinuses, present at birth, grow proportionally with the child. Maxillary sinuses, also present at birth, reach adult size by 4 years of age. The sphenoid sinuses begin to develop around 2 years of age, are functional by age 5, and fully mature by age 12. Finally, the frontal sinuses are first evident by age 6–8 years, not fully maturing until early adulthood.

Acute bacterial rhinosinusitis is incited by predisposing factors such as viral upper respiratory infections, allergic rhinitis, environmental pollutants, nasal septum anomalies, other craniofacial anomalies, adenoidal hypertrophy, masses, polyps, or the presence of a foreign body. Risk factors include smoking, second-hand smoke exposure, and extensive dental disease. All of these conditions impede mucociliary clearance of sinus secretions. Since the sinus cavities are not sterile sites, stasis of secretions increases the likelihood that resident bacterial flora will overgrow resulting in acute bacterial rhinosinusitis [5, 6].

### 4.6.2 Risk Factors

Acute bacterial rhinosinusitis is most common between 4 and 7 years of age. Children in this age group are old enough to have relatively developed sinuses, yet young enough to experience frequent predisposing viral upper respiratory infections. These upper respiratory infections impede usual sinus clearance. Respiratory viral infections are even more common among children less than 2 years of age, but these younger children have less developed sinuses and wider ostia that facilitate drainage. In addition, younger children will often present earlier with AOM. Treatment of the AOM effectively treats any emerging sinus disease, therefore eliminating the opportunity for the development of acute bacterial sinusitis. A second peak of ABRS occurs during adulthood between 45 and 64 years of age. When the infections become recurrent, it is important to maintain a level of suspicion for the presence of contributing factors such as an anatomic blockage (polyps or a foreign body), gastroesophageal reflux disease, allergic disease, a humoral immune deficiency, cystic fibrosis, ciliary dysmotility, or any other condition that might lead to ongoing sinus inflammation and impaired sinus drainage [5, 6].

### 4.6.3 Microbiologic Causes of Acute Bacterial Rhinosinusitis

The optimal manner in which to determine the precise microbiology of acute bacterial rhinosinusitis is to obtain sinus fluid during the acute infection. Existing data, obtained decades ago, are based largely on studies where needle aspirates were performed on infected maxillary sinuses and the fluid sent to the microbiology laboratory for culture. The technique is modestly invasive and now seldom performed outside of academic settings, clinical trials, and severe or particularly enigmatic cases [7]. Not unexpectedly, the common causes of sinus infections are nearly identical to the list of pathogens that cause AOM since both processes arise from bacteria that normally inhabit the human upper respiratory tract at low concentrations.

The most common bacterial agents of ABRS include *S. pneumoniae*, non-typeable *H. influenzae*, and *M. catarrhalis*. *S. pneumoniae* and non-typeable *H. influenzae* are equally common in the post-pneumococcal vaccine era with each accounting for approximately 30% of cases. Infection with *M. catarrhalis* is less frequent at an estimated 10% of total cases [5, 6]. Formal sinus aspirate studies have reported that approximately 30% of nasal sinus aspirates are culture negative for bacteria [7]. Less common causes of ABRS include *S. aureus* and *S. pyogenes*. Anaerobic bacteria have also been implicated either as a primary pathogen or as co-pathogens in several adult studies including *Prevotella*, *Bacteroides*, and *Peptostreptococcus* species. Anaerobic infection should be suspected if there is evidence of extension from dental disease into the sinuses.

### 4.6.4 Approach to the Diagnosis

The initial presentation of sinusitis varies. A careful history of the clinical course of the symptoms over time, the severity of symptoms, and the presence of fever are key details needed to help distinguish ABRS from the more common viral upper respiratory infections. Symptoms more suggestive of ABRS include fever, headache, facial pain and swelling, and halitosis, while cough, nasal congestion, and sore throat are typically seen during bacterial and viral infections [6] [► Call Out Box 4.2].

**Call Out Box 4.2**
A good general rule of thumb: If more than two mucous membranes are involved during a respiratory infection, the cause is viral, not bacterial. Bacterial infections of the upper respiratory tract tend to be localized. Viral infections can involve the eyes, ears, nose, sinuses, mouth, and pharynx simultaneously.

**Table 4.1** Illness characteristics that assist in distinguishing viral from bacterial sinusitis

| Clinical characteristic | Consider a viral etiology | Consider a bacterial etiology |
|---|---|---|
| Progression of symptoms over time | When severity peaks on day 3 or 4 of the illness, followed by gradually improvement with resolution by day 7–10 | When symptoms persist for more 10 days<br>When initial symptoms are severe and the patient has an ill appearance for 3–4 consecutive days<br>When severity peaks on days 3–4, followed by gradual improvement, but on days 6–7, the symptoms worsen<br>When new-onset fever, headache, or facial pain occurs on day 7 or later of the illness |
| Fever | When fever is absent or low grade only<br>When fever is present only on days 1 and 2 of the illness | When any fever persists for more than 5 days<br>When fever greater than 39 °C persists for 3 days or more<br>When there is new onset of fever more than 7 days into the illness |
| Nasal secretions | When nasal discharge is initially thin and clear, becoming thick and yellow-green mid-illness then resolves | When nasal discharge is initially thin and clear, becoming thick and yellow-green, and persisting for more than 3 days<br>When purulent rhinorrhea is unilateral |

The color of the nasal discharge is sometimes used to justify treatment with antibiotics. Viral upper respiratory tract infections usually begin with symptoms of clear, watery, nasal discharge. As the infection and associated inflammation proceed, the discharge becomes thicker and often takes on a yellow-green color. This change is expected during a viral infection and does not herald the presence of a bacterial process. The change in color and consistency is secondary to innate immune responses to the virus, with recruitment of inflammatory cells, including neutrophils. Neutrophil myeloperoxidase allows for some of the oxygen-free radicals to be converted to hypochlorite. It is the presence of this halogenated compound that renders the color change, not the presence of bacteria. Acute bacterial infections trigger the same innate immune inflammatory pathways, explaining why the discharge seen during a bacterial infection also has a yellow-green color. While the color and consistency of the nasal discharge is not helpful in distinguishing viral from bacterial sinusitis, several characteristics of the infection are. Table 4.1 lists some of the ways in which the viral and bacterial sinus infections can be differentiated from one another on clinical grounds.

**Call Out Box 4.3**

**Reliable Diagnostic Criteria for Acute Bacterial Rhinosinusitis**

History *and* physical examination must demonstrate the presence of sinus inflammation:

- **Persistent Disease**: Symptoms lasting 10–30 days without improvement (10–30 days is acute disease, 30–90 days is subacute disease, 90 days or longer is chronic disease)
  - **OR**
- **Severe Disease**: Severe symptoms at initial presentation with ill appearance, fevers higher than 39 °C, and persistent purulent rhinorrhea for 3–4 days
  - **OR**
- **Worsening Disease**: Symptoms showing improvement on days 6–7 of the illness followed by clinical worsening, including the presence of fever, cough, headache, and recurrence of nasal symptoms

Physical examination findings associated with ABRS include erythema and edema of the nasal turbinates, mucopurulent rhinorrhea, and the presence of postnasal drip. Facial pain and sinus tenderness to palpation are less reliable finding in children, but are quite useful indicators in adolescents and adults. None of the physical examination findings are completely specific to either a bacterial or viral infection. The clues obtained during the history of present illness are often the most important key.

Taking the history of present illness and physical examination findings into account, reliable diagnostic criteria for ABRS have been developed [5, 6] [▶ Call Out Box 4.3].

Imaging is rarely useful in the evaluation of uncomplicated bacterial rhinosinusitis. Plain radiographs or computerized tomography imaging of the sinuses undertaken in the absence of compelling history and severe clinical course is likely to demonstrate misleading results. Mucosal thickening, sinus opacification, and air fluid levels may be present, but none of these findings are specific for bacterial underlying etiology. Sinus abnormalities are typically present on imaging in those who have simple viral upper respiratory infections [5]. In contrast, if bacterial rhinosinusitis is present AND complications or spread to adjacent structures is suspected, imaging is always indicated. Computerized tomography imaging of the sinuses and surrounding structures is first line to define the sinus anatomy and bony structures. If there is suspicion that the process has spread intracranially, magnetic resonance imaging of the brain should be considered.

Laboratory evaluation, as with imaging, is not warranted during the evaluation of uncomplicated ABRS. However, if the patient is ill appearing, is immunocompromised, and fails antibiotic treatment, or local extension of the infection is suspected, a sinus aspirate may be warranted. When obtained, the sample is typically sent for Gram stain, aerobic and anaerobic cultures with susceptibility testing. The presence of more than 10,000 colony forming units of a bacterium is considered clinically significant [5].

### 4.6.5 Differential Diagnosis of Bacterial Rhinosinusitis

The differential diagnosis of bacterial rhinosinusitis includes viral upper respiratory infection(s), allergic rhinitis, a local reaction to environmental pollutants, the presence of a nasal foreign body, and adenoidal hypertrophy or infection. If the chief complaint is a prolonged cough illness, infection with *Bordetella pertussis* should also be considered.

### 4.6.6 Treatment of Bacterial Rhinosinusitis

Treatment of bacterial rhinosinusitis is dependent on the clinical course of the illness. Subacute, recurrent, and chronic bacterial rhinosinusitis all warrant prompt antibiotic treatment. In contrast, "persistent" ABRS may be followed with clinical observation for up to 3 days. If symptoms continue or worsen during the observation period, antibiotic therapy is initiated. An observation course must be discussed in detail with patient and indications for returning to care must be explained [5, 6].

First-line antibiotic treatment options for ABRS include either amoxicillin or amoxicillin with clavulanic acid. The use of amoxicillin alone raises concerns regarding coverage of beta-lactamase-producing organisms such as non-typeable *H. influenza*, *Moraxella catarrhalis*, *S. aureus*, and most oral anaerobes. However, rates of clinical failure with amoxicillin alone are low, and amoxicillin boasts a long history of safety and tolerability. Amoxicillin-clavulanate provides broader antimicrobial coverage but can cause gastrointestinal side effects and is less palatable in suspension formulations used for young children. Therefore, either medication can be considered first line in the treatment of uncomplicated bacterial rhinosinusitis.

Certain conditions increase the risk for treatment failure on amoxicillin alone and warrant amoxicillin-clavulanate as the preferred first-line treatment. Included in this group are patients with immune-compromising conditions, those who are incompletely immunized, patients who have received antibiotics during the last 4 weeks or recently required hospitalization, and those with chronic bacterial rhinosinusitis [6]. If multidrug-resistant *S. pneumoniae* is suspected or confirmed as the etiologic pathogen, a third-generation cephalosporin (cefdinir, cefixime, or ceftriaxone) or quinolone class antibiotic, such as levofloxacin, may be necessary [6].

Patients with non-type 1 penicillin hypersensitivity will most likely tolerate advanced-generation cephalosporins without allergic manifestations. Those with type 1 penicillin allergy warrant treatment with a non-penicillin alternative such as levofloxacin, clindamycin, or linezolid [5].

If the illness severity warrants inpatient treatment, intravenous antibiotic regimens with antimicrobial spectra of activity that encompass all of the usual suspects include ampicillin-sulbactam, cefotaxime, ceftriaxone, or levofloxacin. In circumstances where intravenous treatment failure is suspected, multidrug-resistant *S. pneumoniae* should be considered as a potential cause while also referring the patient for surgical consultation to determine if a drainage procedure might facilitate improvement. While awaiting surgical advice, vancomycin can be added to the antibiotic regimen to broaden coverage that includes highly resistant *S. pneumoniae* and methicillin-resistant *S. aureus*. Intravenous metronidazole can also be considered to include coverage for the most resistant anaerobes including *B. fragilis* [5].

Adjunctive therapies to treat nasal symptoms, such as intranasal steroids, saline irrigation or lavage, mucolytics, decongestants, and antihistamines, lack a robust evidence basis, but remain common practices by patients and providers.

### 4.6.7 Complications of Bacterial Sinusitis

Complications of bacterial sinusitis occur when the infection extends to adjacent structures. Localized spread of sinus disease may result in periorbital or orbital cellulitis. Bony involvement may include the formation of a subperiosteal abscess. Orbital extension should be suspected when there is local tissue swelling and edema in the periorbital area. Intracranial extension can include septic cavernous sinus thrombosis, meningitis, brain abscess, or osteomyelitis of the frontal bone. Intracranial disease should be considered if the patient develops persistent and severe headache, mental status changes, focal neurologic examination findings, or persistent emesis.

**Case Study**

**Practical Example**

**Case 1**

A 7-year-old boy presents to the office for a 14-day history of illness that began with cough, rhinorrhea, and complaints of a sore throat. Symptoms gradually worsened for the first few days, but began to improve on day 6. His parents assumed this had been "a typical cold." On day 7 of illness, the boy's symptoms worsened. His cough and rhinorrhea persisted, but secretions became thick and purulent again. He developed new facial pain, fevers to 39 °C, and general malaise. The day prior to the current office visit, the patient began to complain of right eye pain. On physical examination, he appears tired. The right eyelid and surrounding skin is red and swollen. His extraocular movements are intact, but he complains of discomfort when moving his right eye. He also complains of pain during gentle retropulsion. The conjunctivae are clear and there is no chemosis [▶ Call Out Box 4.4]. His nares show purulent rhinorrhea. The TMs are unremarkable. The oropharynx is erythematous with postnasal drainage present. The nasal turbinates are erythematous and edematous.

- What characteristics of this presentation help you distinguish between viral and bacterial sinusitis?
- How would you classify his sinusitis?
- Would you prescribe antibiotics?
- Is any other evaluation warranted? Why or why not?

**Discussion**

The child's early illness included symptoms consistent with a "common cold" of viral etiology. Careful consideration of the clinical course shows that he developed new and more severe symptoms at the time one would expect a typical viral upper respiratory infection to resolve. The new symptoms of fever, headache, and purulent rhinorrhea suggest the evolution of acute bacterial rhinosinusitis (ABRS). In addition, his symptoms have persisted for 14 days. His presentation is best classified as "worsening" acute bacterial rhinosinusitis. This classification warrants initiation of antibiotic therapy. In addition, his report of new-onset eye pain and the findings of periorbital inflammation and discomfort with ocular movement raise suspicion for early extension of the infection to the orbital space. These findings should prompt consideration of inpatient antibiotic therapy and sinus and orbital computerized tomography imaging to evaluate for the presence of intraorbital infection.

**Call Out Box 4.4**

Chemosis is a term used to describe edema of the bulbar conjunctivae. It is usually easiest to appreciate at the limbus, where the bulbar conjunctiva is elevated above the plane of the cornea. Chemosis is a nonspecific finding, but does herald the presence of significant eye irritation.

## 4.7 Mastoiditis

### 4.7.1 Introduction

Mastoiditis is a suppurative infection of the mastoid air cells that most often presents as a secondary complication of otitis media. Its presentation and progression can be acute and require hospitalization and urgent surgical intervention. Routine vaccination against *S. pneumoniae* has reduced the incidence of AOM and led to a decrease in the frequency of mastoiditis in the past decade.

## 4.8 Definitions

**Mastoiditis** – A suppurative bacterial infection of the mastoid air cells

**Acute mastoiditis** – Mastoiditis with symptom duration of less than 1 month

**Coalescent mastoiditis** – Infectious destruction of thin bony septae between mastoid air cells

**Subacute or masked mastoiditis** – A low-grade persistent middle ear and mastoid infection with destruction of the bony septae between the air cells

**Chronic mastoiditis** – Mastoiditis with symptoms exceeding 1 month in duration

## 4.9 Basic Concepts

### 4.9.1 Pathophysiology

The mastoid sinuses are networks of air cells divided by bony septae located in the posterior portion of both temporal bones. The space connects to the middle ear by a bony passage that is present at birth and increases in size until approximately 2 years of age. As the bony passages grow, they become lined with epithelium contiguous to the middle ear space. This continuity of epithelium allows for the possibility for infections of the middle ear to spread to the mastoid. The mastoids are bordered anteromedially by the middle ear and ossicles, the facial nerve, the bony portion of the EAC, the jugular vein, and the internal carotid artery and medially by the inner ear. The sigmoid sinuses are immediately posterior to the mastoids. The cranial fossa sits above, and the soft tissue and muscles of the lateral neck sit below the mastoids on both sides [8, 9].

Mastoiditis is invariably preceded by inflammation and effusion in the middle ear space. The presence of the effusion creates increased pressure between the middle ear and the mastoid air cells. Untreated spread of infection from the middle ear to the mastoid air cells results in resorption of the thin dividing bony septae and osteomyelitis of surrounding temporal bone.

### 4.9.2 Risk Factors for the Development of Mastoiditis

As mastoiditis is a secondary complication of AOM, the two infectious processes share the same set of risk factors. Those at risk for severe mastoiditis include patients with immunodeficiencies, functional or anatomic asplenia, and chronic heart or lung disease. Patients who are underimmunized or unimmunized against *S. pneumoniae* are also at increased risk. Individuals with cochlear implants are at risk for hardware-based infections [8].

### 4.9.3 Microbiologic Causes of Mastoiditis

The most common causes of acute mastoiditis include *S. pneumoniae*, *S. pyogenes*, and *S. aureus* (including methicillin-resistant strains). Less common etiologies include *P. aeruginosa* and other Gram-negative bacteria, non-typeable *H. influenzae*, and resident anaerobes of the oropharynx. *Mycobacterium tuberculosis* is an unusual cause

of mastoiditis but should be considered as a possibility when the illness is diagnosed in individuals who live or have lived in TB endemic areas of the world.

Chronic mastoiditis is most frequently caused by *P. aeruginosa*. Other pathogens to consider when the infection presents as a chronic process include other Gram-negative bacilli, *S. aureus*, and anaerobes [8].

### 4.9.4 Approach to the Diagnosis of Mastoiditis

Acute mastoiditis presents with abrupt onset of fever, otalgia, and a red, swollen postauricular area. The pathophysiology dictates that these symptoms follow a recent middle ear infection. If the initial AOM was treated with antibiotics, there may be an interval of improvement followed by an abrupt worsening of symptoms. The physical examination reveals an abnormal middle ear consistent with AOM. Otorrhea is present in approximately half of the cases because the TM has perforated under the pressure of the infected space. The affected ear will show edema and erythema of the posterior auricular area. The pinna begins to protrude due to edematous displacement. As the infection progresses, fluctuance may develop in the postauricular area over the mastoid air cells.

Chronic mastoiditis is preceded by long-standing middle ear disease. Fevers and postauricular erythema and swelling become evident as the infection progresses. Chronic mastoiditis should be suspected when a patient experiences long-standing TM perforation with chronic otorrhea. Due to the chronicity of the process, the patient may also complain of hearing loss [8, 9].

The diagnosis of mastoiditis is based on the classic clinical signs and symptoms. Once the diagnosis is established, obtaining fluid for microbiologic culture is important to help guide definitive treatment. Samples can be obtained via tympanocentesis or, more commonly, from a mastoid sample collected during surgical debridement. Biologic samples should be sent for Gram stain and aerobic and anaerobic cultures with susceptibility testing. Acid-fast cultures should be requested in cases where tuberculosis is a possibility [8].

Imaging should be used in cases where mastoiditis has been diagnosed clinically as the findings will help to guide decisions regarding surgical care. In the absence of objective physical examination findings of mastoiditis, the presence of opacifications in the mastoid air cells is nonspecific since the finding is also common in uncomplicated serous otitis media and during uncomplicated AOM [10]. When mastoiditis is clinically suspected, computerized tomography scanning (CT) is preferred to evaluate the bony structures. Classic CT findings of mastoiditis include mastoid air cell opacifications, resorption of the bony septae, and coalescence of air cells. CT may also be indicated in patients with AOM that has been unresponsive to antibiotic therapy to rule out the development of secondary mastoiditis. If intracranial or soft tissue complications are suspected, magnetic resonance imaging (MRI) is preferred [8]. Symptoms suggestive of an intracranial complication include focal deficits on neurologic examination, hearing changes, vertigo, meningeal signs, or altered mental status.

### 4.9.5 Differential Diagnosis of Mastoiditis

Scalp infection, periauricular cellulitis, extension of otitis externa, and perichondritis of the auricle may all present with posterior auricular erythema and edema. Parotid swelling secondary to mumps may displace the pinna, but the direction of deviation is superiorly rather than inferiorly seen with mastoiditis [8].

The differential diagnosis of abnormal findings of the mastoid air cells by CT in the absence of objective physical examination findings of mastoiditis includes underaerated or sclerotic air cells due to prior AOM and OME.

### 4.9.6 Treatment of Mastoiditis

All cases of mastoiditis are potential candidates for surgical intervention, and all cases require treatment with antibiotics. Antibiotic alone may be appropriate if the illness presents with focal erythema and edema, but without fluctuance or signs of adjacent spread. Antibiotic therapy in combination with surgical intervention is necessary if fluctuance is present, there is a history of chronic otorrhea, or the patient has developed focal neurologic signs and symptoms such as vomiting, nystagmus, vertigo, or other signs of intracranial disease. Surgical intervention may be fairly straightforward with tympanocentesis or placement of tympanostomy tubes or quite extensive with open debridement of the infected mastoid tissue and adjacent structures.

The initial antibiotic therapy should be administered parenterally. The typical duration of therapy is a minimum of 3 weeks. Depending on the clinical response, the antimicrobial susceptibilities, and the likelihood of adherence, some patients may complete therapy with oral antibiotics. The first-line empiric choice antibiotic for the treatment of acute mastoiditis is typically a medication in the penicillin or cephalosporin class. If the initial presentation is severe, vancomycin is also utilized to ensure coverage against methicillin-resistant *S. aureus* and highly resistant *S. pneumoniae* strains.

Chronic mastoiditis is treated empirically with a modified penicillin in combination with a β-lactamase inhibitor, such as ampicillin plus sulbactam or piperacillin plus tazobactam in combination with gentamicin. This combination provides coverage against, *P. aeruginosa*, and other Gram-negative bacilli and anaerobes. In patients with recurrent AOM and a strong suspicion of *P. aeruginosa*, piperacillin-tazobactam, ceftazidime, *or* cefepime can be used along with clindamycin [8].

The prognosis of mastoiditis is good if the disease is diagnosed and treated before a more serious complication develops. Increasing rates of morbidity and mortality are seen when the infection results in septic thrombosis of the cavernous sinus and/or spread to the temporal lobe of the brain [11].

### 4.9.7 Complications of Mastoiditis

As many as 20% of mastoiditis cases are associated with complications. Infections caused by *S. pyogenes* and *S. aureus* can be particularly aggressive. Interestingly, patients who have recently been treated with antibiotics for AOM have some of the highest rates of complications. This suggests that causative bacteria are particularly pathogenic or have become resistant to more conservative treatments [11]. Known complications involve contiguous spread of the infection to adjacent structures and include subperiosteal abscesses, Bezold's abscesses (infection of the sternocleidomastoid and trapezius muscle attachments), facial nerve paralysis, meningitis, subdural empyema, brain abscess, venous sinus thrombosis, labyrinthitis, temporal bone osteomyelitis, cerebrospinal fluid otorrhea, or conductive hearing loss secondary to destruction of the bony ossicles. Progressive disease can lead to systemic infection with bacteremia and distal septic emboli. A rare but classic complication known as Gradenigo's syndrome is diagnosed when there is petrositis with associated otitis media, ipsilateral medial rectus palsy, eye pain, and possible additional cranial nerve abnormalities [8].

**Case Study**

**Practical Example**

**Case**

A 2-year-old boy presents with redness around his ear. Two weeks prior, he had a "cold" with mild symptoms of rhinorrhea and cough. Seven days into his illness, he developed fevers and began tugging on his right ear. His provider diagnosed him with right AOM and treated him with a 10-day course of amoxicillin. Two days into his course of amoxicillin, he seemed to improve and his fevers resolved. Two days after he completed his antibiotic course, his fevers returned and his mother noticed redness and swelling behind his right ear. On physical examination, the boy appeared fussy and slightly ill. He had clear rhinorrhea. His left EAC and TM were unremarkable. His right TM showed dullness and erythema with visible pus behind it. His right EAC was mildly erythematous and edematous. Manipulation of the right pinna and palpation of the posterior auricular area were quite painful. The postauricular area was erythematous and edematous, but without fluctuance. The right pinna was slightly displaced anteriorly.

- What is the boy's diagnosis?
- Is imaging warranted?
- Should his management include antibiotics, surgery, or both?
- Is inpatient or outpatient treatment more appropriate in this clinical setting?

**Discussion**

The patient's age, preceding AOM, and physical examination findings are consistent with acute mastoiditis. His presentation was relatively recent in onset. He does not have fluctuance on physical examination or signs and symptoms of adjacent spread. A case could be made for imaging to confirm mastoid findings and rule out any progressive bony disease. His initial management should include treatment with intravenous antibiotics in the inpatient setting.

## 4.10 Exercises

Please refer to the supplementary information section for answers to these exercises.

Match the clinical scenario with the most likely pathogen. Each pathogen may be used once, more than once, or not at all.

| Pathogen | Characteristic finding |
|---|---|
| 1. Most common bacterial cause of acute otitis media | A. *Mycobacterium tuberculosis* |
| 2. Classic bacterial cause of concurrent otitis and conjunctivitis | B. *Streptococcus pyogenes* |
| 3. Most common vaccine preventable cause of otitis, sinusitis, and mastoiditis | C. *Moraxella catarrhalis* |
| 4. Gram-positive cause of mastoiditis that produces a β-lactamase | D. *Haemophilus influenzae*, nontypeable |
| 5. An uncommon cause of mastoiditis associated with ossicle damage and hearing loss that should be considered in refugees from Africa and Asia | E. *Streptococcus pneumoniae*<br>F. *Staphylococcus aureus* |

## 4.11 Summary

Otitis, sinusitis, and mastoiditis represent a spectrum of otolaryngologic infections that cause signs and symptoms overlapping with the ubiquitous viral upper respiratory infection or "common cold." Clinical guidelines for each stress careful consideration of diagnostic criteria, vigilance for the development of complications, the most appropriate antibiotic options, and when necessary, appropriate surgical interventions.

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### Further Reading

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# Pharyngitis and Pharyngeal Space Infections

## Fever, Sore Throat, Difficulty Swallowing

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**Learning Objectives**

- Understand that most cases of pharyngitis are caused by viruses and will resolve with supportive care alone.
- Describe common symptoms associated with a case of uncomplicated pharyngitis.
- Recognize the warning signs of a more serious infection requiring prompt attention such as a deep neck space infection, epiglottitis, or Ludwig's angina.
- Recognize some of the predisposing factors associated with atypical causes of pharyngeal infections.



## 5.1 Introduction to the Problem

Acute pharyngitis affects a significant number of people across the United States and the world each year and impacts patients from all age groups. It accounts for 1–2% of all ambulatory visits and causes missed days from work and school [1, 2]. The cause is typically infectious in etiology, with viruses being most common pathogens involved, followed by bacteria, fungi, and rarely parasites. Noninfectious conditions may cause pharyngitis, and if symptoms are not self-limiting or do not respond to appropriate medical treatment, they should be considered. Symptoms range from a mild sore throat lasting for several days to severe manifestations that threaten the patency of the airway. Deep neck space infections can also extend directly into the mediastinum or the lungs causing life-threatening mediastinitis or pneumonia, underscoring the importance of early recognition and treatment.

## 5.2 Definitions

Important cavities, spaces, and structures in the head and neck. See ◘ Figs. 5.1, 5.2, and 5.3 for pictographic demonstrations of select neck spaces.

### 5.2.1 Cavities of the Head and Neck

**Oral cavity** – The anatomic cavity bound anteriorly by the lips, laterally by the buccal mucosa, inferiorly by the floor of the mouth, superiorly by the hard palate, and posteriorly by the anterior tonsillar pillar, circumvallate papillae, and junction of the hard and soft palates.

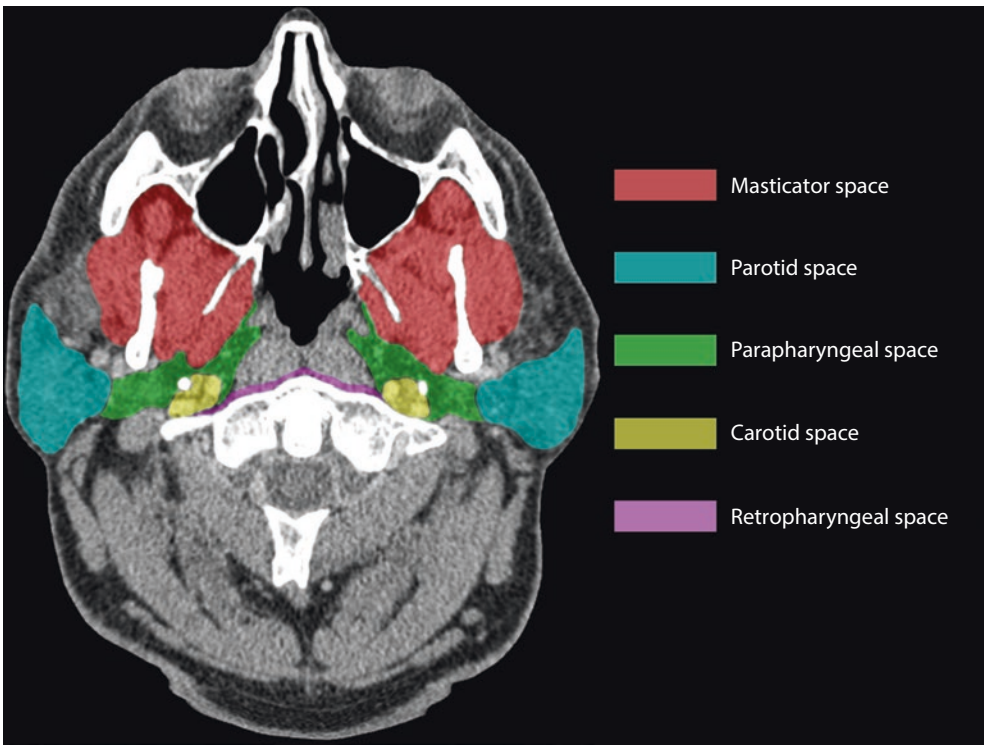
**Nasopharyngeal cavity** – The anatomic cavity bound by the skull base superiorly, the soft palate inferiorly, the nasal choanae anteriorly, the arch of the atlas posteriorly, and the eustachian tubes laterally.

**Oropharyngeal cavity** – The anatomic cavity bound anteriorly by the anterior tonsillar pillar, the circumvallate papillae, and the junction of the hard and soft palates. The superior and middle constrictors form the posterior and lateral boundaries, and the soft palate forms the superior boundary. The tongue base and hyoid bone form the inferior boundary.

**Hypopharyngeal cavity** – The anatomic cavity extending from the level of the hyoid bone superiorly to the level of the cricoid inferiorly, the larynx anteriorly and cervical vertebrae 3 through 6 posteriorly, and the thyroid cartilage laterally.

### 5.2.2 Spaces of the Head and Neck

**Peritonsillar space** – This anatomic space is bound by the anterior tonsillar pillar anteriorly, the posterior tonsillar pillar posteriorly, the capsule of the palatine tonsil medially, and the superior pharyngeal constrictor laterally. The peritonsillar space is comprised of loose areolar connective tissue in most individuals, but the lingual branch of




◘ **Fig. 5.1** Shown is a normal axial CT scan with intravenous contrast outlining the carotid sheath, parapharyngeal, retropharyngeal, parotid, and masticator spaces

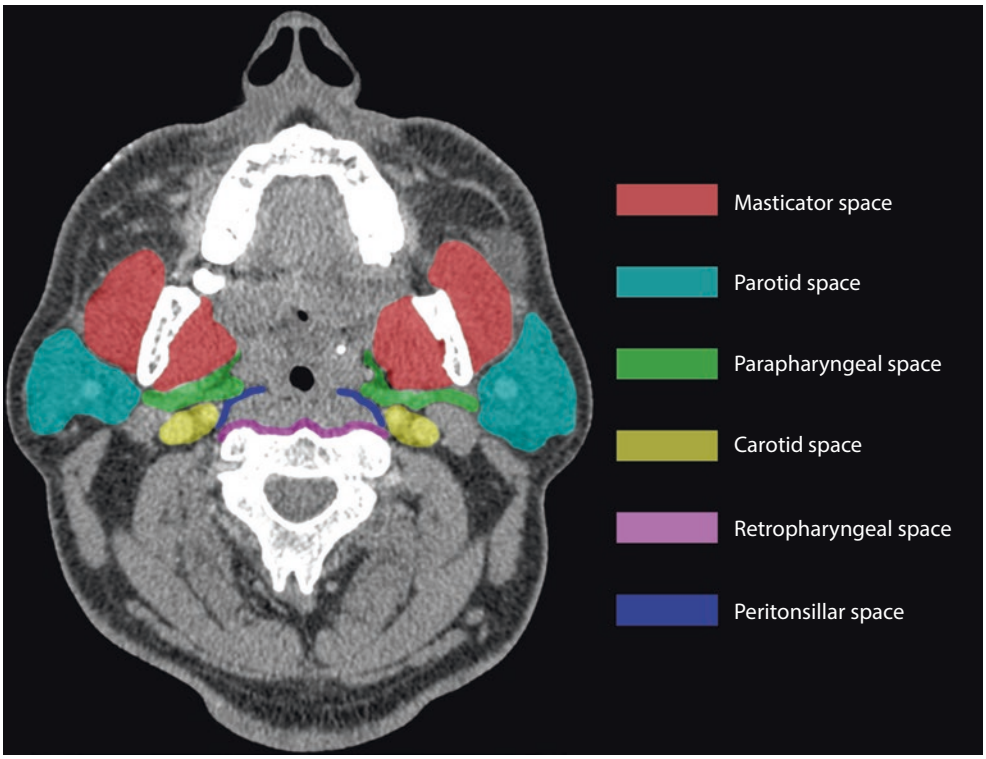



**Fig. 5.2** Shown is a normal axial CT scan with intravenous contrast outlining the spaces outlined in Fig. 5.1 at a more inferior position, now including the peritonsillar spaces

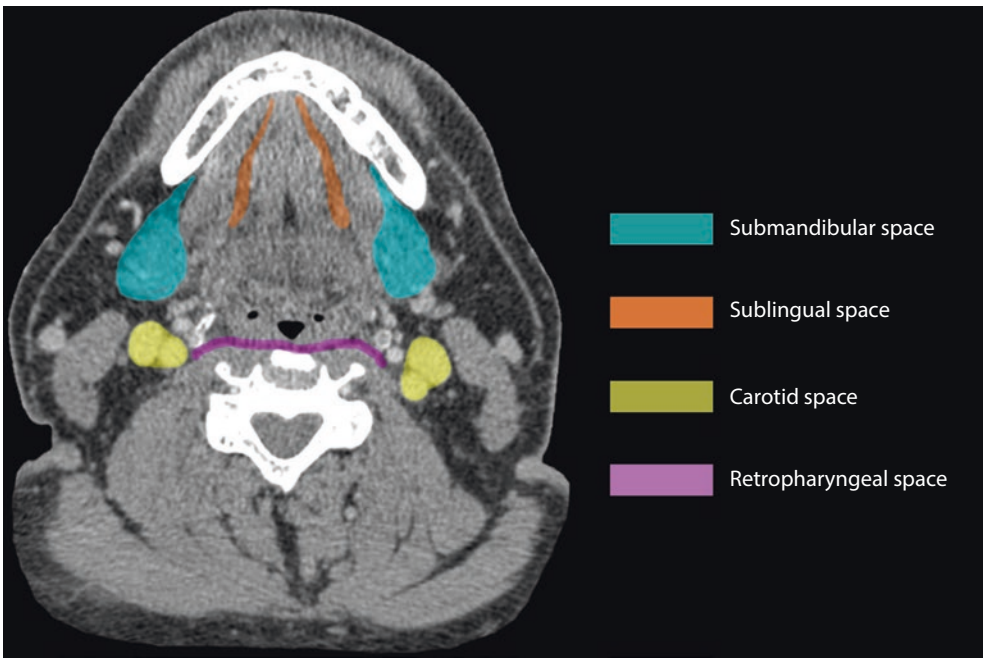



**Fig. 5.3** Shown is a normal axial CT scan with intravenous contrast outlining the carotid sheath, retropharyngeal, sublingual, and submandibular spaces

the glossopharyngeal nerve courses through it in a minority as an anatomic variant. The peritonsillar space communicates with the parapharyngeal space.

**Parapharyngeal space** – This anatomic space is traditionally described as an inverted pyramid lateral to the peritonsillar space and nasopharyngeal cavity. It is bound superiorly by the base of the skull, inferiorly by the greater cornu of the hyoid bone, anteriorly by the pterygomandibular raphe and medial pterygoid, posteriorly by the cervical vertebrae and paravertebral muscles, and laterally by the parotid gland. The parapharyngeal space is further divided into pre- and post-styloid compartments by a band of fascia called the aponeurosis of Zuckerkandl and Testut, which connects the styloid process of the temporal bone to the tensor veli palatini. The pre-styloid compartment contains fat, muscles, lymph nodes, the deep lobe of the parotid gland, the internal maxillary branch of the external carotid artery, and several branches of cranial nerves. The post-styloid compartment contains the internal carotid artery, internal jugular vein, sympathetic chain, lymph nodes, and cranial nerves IX through XII. This space communicates with the submandibular space, peritonsillar space, retropharyngeal space, and sublingual space.

**Retropharyngeal space** – As its name implies, this anatomic space lies posterior to the pharynx. It is bound anteriorly by the visceral

division of the middle cervical fascia, posteriorly by the alar division of the deep cervical fascia, laterally by the carotid sheaths, superiorly by the skull base, and inferiorly to the mediastinum. This space typically only contains loose areolar connective tissue and lymph nodes, but may contain the internal carotid arteries as an anatomic variant referred to as retropharyngeal carotids. Infections in this space are particularly concerning due to their ability to spread inferiorly to the mediastinum or superiorly to the skull base. The retropharyngeal space communicates with the parapharyngeal space.

**Danger space** – This anatomic space lies just posterior to the retropharyngeal space, and like the retropharyngeal space, it extends from the skull base to the mediastinum. It is bound posteriorly by the prevertebral fascia and laterally by the transverse processes of the vertebrae. It is called the "danger space" because bacterial infections in this area can spread to the thorax very quickly.

**Prevertebral space** – This anatomic space lies posterior to the prevertebral fascia and danger space and extends from the skull base to the coccyx. It is bound posteriorly by the vertebral bodies and laterally by the transverse processes of the vertebrae. It contains muscles, the vertebral arteries and veins, and the phrenic nerve and roots of the brachial plexus.

**Submandibular space** – This anatomic space is bound anteriorly by the anterior belly of the digastric muscle, posteriorly by the posterior belly of the digastric muscle, medially and superiorly by the mylohyoid muscle, laterally by the platysma, and inferiorly by the hyoid bone. It contains the submandibular gland, lymph nodes, facial vessels, and hypoglossal nerve. It communicates with the parapharyngeal and sublingual spaces.

**Sublingual space** – These anatomic paired spaces are each bound superiorly by the floor of the mouth, inferiorly by the mylohyoid muscle, anteriorly and laterally by the mandible, posteriorly by the hyoid bone, and medially by extrinsic muscles of the tongue. They communicate with each other beneath the lingual frenulum, and they communicate with the submandibular and parapharyngeal spaces.

**Masticator space** – This anatomic space is bound medially by the fascia medial to the pterygoid muscles, laterally by the mandibular ramus, superiorly by the base of the skull, inferiorly by the lower border of the mandible, anteriorly by the pterygomandibular raphe, and posteriorly by the parotid gland. It is subdivided into the masseteric and pterygoid spaces, which are delineated by the superficial layer of the deep cervical fascia. The masticator space contains muscles of mastication, the ramus and posterior body of the mandible, the inferior alveolar nerve, and the internal maxillary branch of the external carotid artery. This space communicates with the parapharyngeal space, submandibular space, and sublingual spaces.

### 5.2.3 Important Structures of the Head and Neck

**Waldeyer's tonsillar ring** – An arrangement of lymphoid tissue in the pharyngeal cavity that forms a circular loop consisting of the lingual tonsils, the adenoids, and the palatine tonsils.

**Carotid sheath** – Paired anatomic structures lateral to the retropharyngeal space extending from the base of the skull to the sternum containing the carotid arteries, internal jugular veins, cranial nerves IX through XII, and the sympathetic trunk.

## 5.3 Basic Concepts

The vast majority of patients with pharyngitis have mild to moderate illness that is either self-limiting or rapidly responsive to appropriate antibiotic treatment. The initial approach to a patient with suspected pharyngitis or parapharyngeal space infection, however, should always include a careful assessment for signs of airway compromise. Findings of concern include respiratory distress, drooling, orthopnea, muffled speech ("hot potato voice"), difficulty turning the head, and elevation of the tongue and floor of the mouth. A patient in acute distress due to a retropharyngeal abscess, for example, may exhibit opisthotonic posturing with neck hyperextension. These findings should prompt immediate transfer to an emergency department for evaluation with flexible laryngoscopy, if expertise is available. In extreme cases, emergency endotracheal intubation or surgical interventions are necessary to establish and protect the airway. Intravenous broad-spectrum antibiotics should also be administered as soon as possible in critical patients. The laboratory evaluation typically includes a complete blood count, erythrocyte sedimentation rate, C-reactive protein, blood cultures (both aerobic and anaerobic), and pharyngeal, laryngeal, tracheal, or epiglottis cultures for those undergoing a procedure that protects their airway. Imaging should be deferred for the critically ill patient until their airway has been secured. The recognition of and immediate intervention for a compromised airway are always the top priority (*a*irway, *b*reathing, *c*irculation, in that order).

In the stable patient, the extent of the diagnostic evaluation depends on the history and physical examination findings. The history should include a determination of the onset, progression and duration of symptoms, the quality and severity of any associated pain, and factors that aggravate or alleviate the discomfort. The presence or absence of associated symptoms, such as fever, cough, dysphagia, trismus, nasal congestion, rhinorrhea, neck pain, or dental pain, should be noted. Symptoms that are more prominent on one side suggest the presence of an abscess or phlegmon. The presence or absence of underlying chronic medical conditions, particularly those that are associated with immunosuppression such as diabetes, HIV infection, collagen vascular diseases, or malignancy, should be determined. A recent history of dental work, endotracheal intubation, surgery on the upper aerodigestive tract, and/or penetrating neck trauma is also important to obtain [► Call Out Box 5.1].

**Call Out Box 5.1**
Deep neck space infections can cause airway compromise. It is important to recognize signs of impending respiratory failure and establish a safe airway before any other interventions are started.

## 5.4 Infectious Causes of Pharyngitis and Parapharyngeal Infections

Infectious etiologies of pharyngitis and parapharyngeal infections include viruses, bacteria, fungi, and parasites. By far, viral infections are the most common. Susceptibility to

the different infectious agents varies by age, medical comorbidities, and exposures, so a complete history is necessary to guide clinical decision-making or to raise the possibility that a more unusual pathogen may be responsible for a patient's illness. Rarely, autoimmune disorders, previously unrecognized immunodeficiency, anatomic abnormalities, or malignancies can exacerbate or mimic symptoms of neck infections. Patients with persistent symptoms, who do not respond to empiric therapy based on the suspected diagnosis of infection, should undergo additional diagnostic testing to evaluate for the presence of the more unusual infectious and noninfectious entities.

### 5.4.1 Viruses as Causes of Pharyngitis and Related Infections

Most cases of pharyngitis and tonsillopharyngitis are caused by viruses [3]. Since effective antiviral medications are not available for the majority of relevant viruses, treatment is nearly always focused on reducing pain and fever. Patients may refuse to eat and drink for a sufficient period of time, making intravenous fluids necessary to reestablish and maintain hydration. Table 5.1 lists the more common causes of viral pharyngitis. Pharyngitis is usually one of several symptoms that patients complain about when infected with any of the common "cold and flu" viruses. Since respiratory viral pathogens do not discriminate between mucosal targets, symptoms of conjunctivitis, rhinitis, and laryngitis with cough and/or hoarseness are typically present along with the sore throat. If only a single mucous membrane appears to be involved, a bacterial cause should be considered.

Any of the respiratory viral infections can be associated with fever, especially in young children, but influenza viruses and adenoviruses are notorious for causing fevers at any age. Viral pharyngitis is a clinical diagnosis. Respiratory virus diagnostic testing is available, however, for patients with severe infection or confusing atypical presentations. At the present, polymerase chain reaction (PCR)-based testing can be performed on nasopharyngeal or oropharyngeal samples. Some platforms allow for the rapid diagnosis of more than a dozen viruses simultaneously.

Respiratory "cold and flu" viruses account for most cases of viral pharyngitis, but several others are also worthy of discussion. For example, exudative pharyngitis is a classic finding in patients with infectious mononucleosis, a syndrome most commonly caused by Epstein-Barr virus (EBV). The syndrome is diagnosed clinically in patients with exudative pharyngitis, lymphadenopathy, and splenomegaly. Fevers are common and can persist for 3 weeks or longer. Patients with infectious mononucleosis also complain of extreme fatigue, sometimes lasting for months. The diagnosis of EBV-associated infectious mononucleosis is confirmed serologically by testing for IgM and IgG antibodies against the EBV viral capsid antigen (EBV VCA IgM and IgG). The detection of EBV VCA IgM is consistent with acute EBV infection. A rapid screening test for EBV infection, the serum heterophil antibody assay, is still used commonly. Results should be interpreted with caution since the assay is both less sensitive and less specific than antibody testing. Treatment for EBV infection is primarily supportive care. In severe cases, the combination of pronounced pharyngeal swelling and impressive cervical adenopathy may lead to concerns for impending airway compromise. Under such circumstance, systemic glucocorticoids can be administered to reduce the swelling, perhaps avoiding the need for a medical or surgical procedure to maintain airway patency. The use of glucocorticoids should otherwise be avoided because of their immunosuppressive activity.

The second most common cause of infectious mononucleosis is cytomegalovirus. The clinical presentation can be identical to that seen from EBV, but the EBV-specific serologic testing will not indicate an acute EBV infection, and the rapid heterophil antibody assay will be negative. A positive CMV IgM antibody test confirms the diagnosis of acute CMV infection.

**Table 5.1** Typical causes of viral pharyngitis

| Viruses | Are they typical "cold and flu" viruses? | Is effective antiviral treatment available? |
|---|---|---|
| Rhinoviruses | Yes | No |
| Adenoviruses | Yes | No |
| Coronaviruses 229E, HKU1, OC43, NL63 | Yes | No |
| Respiratory syncytial virus | Yes | No |
| Parainfluenza viruses 1 through 4 | Yes | No |
| Influenza A and B viruses | Yes | Yes |
| Human metapneumovirus | Yes | No |
| Echoviruses | Yes | No |
| Coxsackie A and B viruses | Yes | No |
| Enteroviruses | Yes | No |
| Epstein-Barr virus | No | No |
| Cytomegalovirus | No | Yes, but not used for pharyngitis |
| Human immunodeficiency virus (HIV) | No | Yes[a] |
| Herpes simplex viruses 1 and 2 | No | Yes, but seldom used for pharyngitis |

[a]Antiretroviral medications are not typically used specifically for the symptoms of pharyngitis associated with the acute retroviral syndrome of newly acquired HIV infection

Acute infection with human immunodeficiency virus (HIV) can also present with an infectious mononucleosis-like illness called acute retroviral syndrome. The syndrome is characterized by self-limiting fevers, malaise, myalgias, pharyngitis, and cervical lymphadenopathy occurring several days to several weeks after exposure. HIV should, therefore, be suspected in all patients who present with an infectious mononucleosis syndrome. The diagnosis of HIV infection is made using combined, fourth-generation tests designed to detect both HIV-specific antibodies and HIV p24 antigen. Patients who are infected recently, who have not yet seroconverted by making anti-HIV antibodies, often have detectable circulating HIV p24 antigen. A major advantage of fourth-generation testing is the ability to detect HIV p24 antigen and diagnose HIV infection as early as 1 week after exposure. The earliest detectable anti-HIV antibody is present after 2–4 weeks.

Herpes simplex virus (HSV) types 1 and 2 can also cause impressive pharyngitis. Patients may present with fevers, malaise, headaches, cervical lymphadenopathy, and sore throat with or without the formation of vesicles visible in the oropharyngeal cavity. When vesicles are seen, they tend to rupture forming ulcerative plaques with grayish exudate.

Infants and young children who develop primary oral HSV infection typically present with gingivostomatitis. A very painful vesicular eruption is seen on the mucous membranes in the anterior part of the mouth including the gingiva and the tongue, with lesions extending onto the lips. In contrast, primary oral HSV infection in adolescents and adults most commonly presents as severe pharyngitis. Since vesicles are not always present, it is likely that a substantial number of such cases go undiagnosed. The diagnosis of HSV pharyngitis (or gingivostomatitis) is made either by HSV-specific polymerase chain reaction (PCR)-based testing or by viral culture of material collected by swabbing the affected mucous membranes. In immunocompetent patients, oral HSV infections will eventually resolve spontaneously; however, outpatient treatment of antiviral medication acyclovir, or one of its derivatives, offers the potential to reduce symptoms, reduce virus shedding, and hasten recovery. Immunosuppressed patients who develop active HSV disease benefit most by treatment with intravenous acyclovir.

Another group of viruses capable of causing painful vesicular lesions in the mouth are the enteroviruses. The term herpangina is used to describe these lesions when present on the roof of the mouth and in the back of the throat. Despite its name and the vesicular nature of the lesions, herpangina refers to an enteroviral infection, not a herpetic infection. When herpangina is associated with a maculopapular or vesicular rash of the hands and feet, it is referred to as hand, foot, and mouth disease. Among the enteroviruses that cause herpangina with or without the rash, coxsackie A16 is the most notorious because it continues to be responsible for a large number of pediatric cases of hand, foot, and mouth disease each summer during enterovirus season. The diagnoses of herpangina and hand, foot, and mouth disease are easy to make on clinical grounds alone, but if viral diagnostic testing is pursued, PCR testing is preferred. Enterovirus typing is only performed by reference laboratories and usually only for the purposes of outbreak investigations.

### 5.4.2 Fungi as Causes of Pharyngitis and Related Infections

Oral candidiasis, commonly called "thrush," is the most common fungal infection of the upper aerodigestive tract. Thrush leads to white, cheese-like plaques on the tongue and buccal mucosa that are not easily scraped away. Some bleeding may occur if scrapings are done for diagnostic purposes. The diagnosis of oral candidiasis is made clinically; however if scrapings of the affected area are cultured, the yeast *Candida albicans* or a related *Candida* species is recovered. Two less typical presentations of oral candidiasis include the erythematous and the chronic hyperplastic types. Erythematous oral candidiasis presents with a red, very sore oropharyngeal cavity, while chronic hyperplastic candidiasis presents with leukoplakia at the corners of the mouth and tongue. *C. albicans* is a normal flora of the human skin and mucous membranes. When there is a disturbance in immune function or an imbalance in the usual bacteria flora, as occurs with antibiotic use, *C. albicans* can cause infection. Thrush is quite common during the first few months of life, at least in part because of the immaturity of the newborn's cellular immune function. In almost every other instance, *C. albicans* requires a conditional opportunity to cause an *opportunistic* infection. Patients who are being treated with long-term antibiotics or immunosuppressive medications, including glucocorticoids, and those with primary and acquired immune deficiencies commonly develop thrush. Untreated, the infection can progress and extend to posterior pharyngeal cavity structures, the esophagus, and the airway. Pharyngitis secondary to candidiasis can be extremely painful causing severe dysphagia. When oral candidiasis progresses to visibly involve the structures of the posterior oropharyngeal cavity, it is important to consider that it may have also spread to the esophagus, larynx, or trachea. Direct visualization using nasopharyngeal laryngoscopy may be indicated. The presence of advanced oral candidiasis in a patient without known risk factors should always prompt an evaluation for immunocompromising conditions, including HIV infection.

Other fungal infections of the pharynx and parapharyngeal space caused by a variety of opportunistic yeasts and molds have been described as case reports, nearly always in patients with significant immunocompromising conditions.

### 5.4.3 Parasites as Causes of Pharyngitis and Related Infections

Parasitic infections of the pharynx and parapharyngeal spaces are exceedingly rare but should be considered in certain circumstances. In developed countries, infection with *Toxoplasma gondii* has been described in organ transplanta-

tion patients being treated with immunosuppressive medications and in patients with poorly controlled HIV infection. Case reports of pharyngeal space infections caused by tapeworms (*Echinococcus granulosus* and *Taenia solium*), roundworms (*Lagochilascaris minor*), and protozoa (*Leishmania braziliensis* and *T. gondii*) have all been reported to occur. The diagnosis of a parasitic infection of the pharyngeal cavity or parapharyngeal space requires a high index of suspicion, surgical sampling, and expert parasitologists working in the clinical microbiology laboratory. Treatment would depend on the parasite involved, usually in collaboration with experts at the US Centers for Disease Control and Prevention and/or World Health Organization.

## 5.4.4 Bacteria as Causes of Pharyngitis and Related Infections

Bacterial infections are second to viral infections as the most common group of pathogens to cause pharyngitis. *Streptococcus pyogenes*, which is also referred to as group A streptococcus, is the most common bacterial cause of pharyngitis. Bacteria also cause nearly all deep suppurative infections of the head and neck. The deep space infections are often polymicrobial. Culture results are representative of the diverse microbiologic flora of the normal human oropharynx [4–9] (▶ Box 5.1), although virulent pathogens such as *Staphylococcus aureus* and *S. pyogenes* are also identified on a regular basis. The etiologies and sequelae of these infections have been shown which vary by patient characteristics, particularly by age and by the presence of comorbid conditions. For example, dental infections are the most common source and predisposing factor for deep neck space infections in adults, but tonsillitis and pharyngitis are the most common predisposing factor among children [10–12]. Adolescents and young adults have higher rates of peritonsillar abscess compared to the younger children or older adults, while retropharyngeal abscesses are most common in preschool-aged children [13].

### 5.4.4.1 Bacterial Causes of Pharyngitis and Tonsillopharyngitis

Group A streptococcus (GAS) is the most common cause of acute bacterial pharyngitis and tonsillopharyngitis. Less frequent causes are listed in ◘ Table 5.2. Clinically, streptococcal pharyngitis is associated with fever, tender anterior cervical lymphadenopathy, pharyngeal erythema, and tonsillar swelling. Exudate may be seen on the posterior pharyngeal wall and on the tonsils. Streptococcal pharyngitis may also be associated with the presence of palatal petechiae and a skin rash. The diagnosis of GAS pharyngitis is based on both the clinical presentation and the results of laboratory testing. The Centor and modified Centor criteria

**Box 5.1 Bacterial Causes of Deep Neck Space Infections**

**Virulent invasive pathogens that can also be oropharyngeal flora**
- *Staphylococcus aureus*
- *Streptococcus pyogenes* (group A beta-hemolytic streptococcus)
- *Haemophilus influenzae*

**Oropharyngeal flora: facultative anaerobes**
- Viridans group streptococci[a]
- Other *Streptococcus* species
- *Haemophilus parainfluenzae*
- *Moraxella catarrhalis*
- *Eikenella corrodens*
- *Cutibacterium acnes*
- *Mycobacterium* species other than tuberculosis

**Oropharyngeal flora: obligate anaerobes**
- *Fusobacterium necrophorum*
- *Bacteroides fragilis* group[b]
- *Prevotella* species
- *Porphyromonas* species

[a]The viridans group streptococci are alpha-hemolytic *Streptococcus* species, many of which are normal species of the human gastrointestinal tract. There are six major groups: *S. mutans*, *S. salivarius*, *S. anginosus*, *S. mitis*, *S. sanguinis*, and *S. bovis*
[b]The *Bacteroides fragilis* group includes *B. fragilis* (the most common), *Bacteroides distasonis*, *Bacteroides ovatus*, *Bacteroides thetaiotaomicron*, and *Bacteroides vulgatus*

◘ **Table 5.2** Bacterial causes of pharyngitis

| Bacteria | Relative frequency |
|---|---|
| *Streptococcus pyogenes* (group A streptococcus) | Most common |
| *Streptococcus zooepidemicus* and others (group C streptococcus) | Common |
| *Streptococcus dysgalactiae* and others (group G streptococcus) | Common |
| *Mycoplasma pneumoniae* | Common |
| *Arcanobacterium haemolyticum* | Regular |
| *Neisseria gonorrhoeae* | Regular |
| *Fusobacterium necrophorum* | Regular |
| *Corynebacterium diphtheriae* | Rare |
| *Chlamydophila pneumoniae* | Rare |
| *Chlamydia trachomatis* | Rare[a] |
| *Yersinia pestis* | Rare |
| *Francisella tularensis* | Rare (pharyngeal tularemia) |
| *Chlamydophila psittaci* | Rare |

[a]*Chlamydia trachomatis* can be detected regularly from pharyngeal swabs, but is only rarely associated with symptoms of pharyngitis

**Table 5.3** Modified Centor criteria for the clinical diagnosis of streptococcal pharyngitis

| Criteria | Points |
|---|---|
| Absence of cough | 1 |
| Swollen, tender anterior cervical lymph nodes | 1 |
| Temperature >100.4 °F (38 °C) | 1 |
| Tonsillar exudates or swelling | 1 |
| Age | |
| 3–14 years | 1 |
| 15–44 years | 0 |
| 45+ years | −1 |

[a]A score less than 3 does not warrant further testing as the probability of a Group A streptococcal infection is low. A score of 3 or more should warrant further testing with cultures or rapid antigen detection tests and antibiotic treatment if these tests are positive

**Call Out Box 5.2**
Empiric treatment of pharyngitis with antibiotics is no longer recommended. Initiation of antibiotics should be directed by cultures.

(Table 5.3) have been used as diagnostic adjuncts to help clinicians identify patients who are likely to have GAS infection and unlikely to have a viral infection. A score of 0 or 1 on the modified Centor score indicates a low probability of GAS infection, and no further diagnostic testing or empiric antibiotic therapy is recommended. Score of 2 or 3 indicates the possibility of strep throat, so throat cultures are recommended, with initiation of antibiotics if the cultures are positive for group A streptococcus. A score of 4 or more once indicated that empiric treatment with antibiotics should be started while waiting for culture results; however, in recent years, the US Centers for Disease Control and Prevention (CDCP) and national professional societies have since recommended against empiric antibiotic usage [► Call Out Box 5.2]. Antibiotics should only be used when cultures are positive [14, 15]. Overall, evidence has shown only a modest benefit of antibiotics in reducing the duration of a sore throat symptoms; however treatment is highly effective at preventing acute rheumatic fever and reduces the frequency of peritonsillar abscess formation [16]. Antibiotic treatment does not, however, reduce the possibility of developing post-streptococcal glomerulonephritis. Penicillin is the antibiotic of choice for GAS pharyngitis unless the patient is allergic to it. Amoxicillin is an acceptable alternative. Patients who are allergic to, or cannot tolerate, β-lactam antibiotics can be treated with clindamycin, azithromycin, or clarithromycin. Unlike many other common bacterial pathogens, *S. pyogenes* has not developed resistance to β-lactam antibiotics. Resistance to clindamycin is rare in most communities but well described in others. Occasional resistance to azithromycin and clarithromycin is also seen. Clinical treatment failures with penicillin and amoxicillin do occur despite the absence of antibiotic resistance. Such failures are best explained by failure of the penicillin pharmacodynamics, not by a resistance mechanism acquired by the streptococcus.

Some patients develop recurrent GAS pharyngitis and/or tonsillitis because unlike many other common infections, natural disease does not confer protective immunity to reinfection. The American Academy of Otolaryngology clinical practice guidelines for streptococcal pharyngitis advocate for watchful waiting if a patient has had fewer than seven documented episodes of streptococcal pharyngitis in the last year, fewer than five episodes per year for at least 2 years, or fewer than three infections per year for at least 3 years [17, 18]. For patients who do not meet these criteria, tonsillectomy may be offered. In addition, tonsillectomy may be considered in patients with comorbidities, including obstructive sleep apnea, chronic tonsillitis unresponsive to medical therapy, cardiac valvular disease, recurrent febrile seizures, tonsiliths, history of peritonsillar abscess, or allergy/intolerance to antibiotic therapy. Ideally, a tonsillectomy should be performed in the absence of an active infection to reduce the chances of a surgical complication such as postoperative bleeding. Occasionally an emergency tonsillectomy, historically referred to as a quinsy tonsillectomy, needs to be performed because of airway compromise.

### 5.4.5 Deep Neck Space Infections

Deep neck space infections can present as discrete organized abscesses within specific neck spaces, as a soft tissue phlegmons without clearly forming collections of pus, or rarely, as a very rapidly destructive life-threatening process called necrotizing fasciitis. These conditions typically arise from the direct spread of a less serious infectious process present in an adjacent space. Deep neck space infections become particularly concerning when compartments that communicate directly with the mediastinum are involved, such as the retropharyngeal, danger, and prevertebral spaces. Depending on their specific location, these infections can also cause significant airway compromise over a relatively short period of time. The underlying predisposing cause for deep neck space infections varies based on age. Children who develop deep neck infections usually do so after starting with pharyngitis, while the most common initial source of infection in adults comes from an odontogenic process [► Call Out Box 5.3]. The

**Call Out Box 5.3**
Pharyngitis is the most common source for developing deep neck space infections in children, whereas odontogenic infections are the most common underlying source in adults.

microbiology of deep neck space abscesses is often polymicrobial with a mix of aerobic and anaerobic organisms. Box 5.1 includes some of the more common bacterial isolates from deep neck space abscess cultures [11, 19]. Some bacterial species require very specific conditions in order to be successfully cultured in the laboratory and thus are not detected in standard cultures [7]. Evolving changes in the antibiotic susceptibility profiles for several of these bacterial types further complicate approaches to patient management [11, 20, 21].

Differentiating between an abscess and phlegmon on clinical grounds is difficult since both conditions cause sore throat, dysphagia, otalgia, voice changes, and swelling of the neck and oropharyngeal cavity. Abscesses are usually discovered by computed tomography (CT) scan; however the level of suspicion for an abscess is raised if there is marked swelling of the oropharynx or neck or when an infection is not responding to broad-spectrum antibiotics. Abscess formation is the result of the host reaction to an infection and serves to encapsulate the infected area. The lack of blood flow into the abscess, together with the low pH and low or absent oxygen context, can render antibiotics ineffective in treating these infections due to their inability to penetrate the abscess intact at concentrations that are bactericidal.

Three of the more common deep neck space abscesses include peritonsillar abscesses (PTAs), parapharyngeal abscesses, and retropharyngeal abscesses (RPAs). As their names imply, these are conditions where there is abscess formation within their respective deep neck spaces. Because of their proximity to each other and relative ease of bacterial spread between the compartments, it is not uncommon for two or more neck spaces to be involved [13, 22]. For example, Fig. 5.4 shows the CT scan findings from a case of a parapharyngeal abscess with a contiguous RPA.

The clinical presentation of PTAs, parapharyngeal abscesses, and RTAs has many similarities; however there are some distinctions between the three that may help differentiate them. Similarities between the three include the presence of sore throat, dysphagia, voice changes, odynophagia, and, in advanced cases, difficulty breathing. The classic presentation of PTAs also includes a visible, asymmetrical bulge of the tissues on the affected side with deviation of the uvula to the contralateral side, a cellulitic appearance of the anterior tonsillar pillar and lateral soft palate (Fig. 5.5), and trismus. When considering the appearance of a PTA on CT scan (Fig. 5.6), it is easy to imagine the abscess displacing the surrounding tissue and thus creating the bulging appearance of the anterior tonsillar pillar and deviation of the uvula away from the affected side.

Parapharyngeal abscesses can also cause trismus and neck swelling above the level of the hyoid bone. Anterior parapharyngeal space abscesses may result in a bulging appearance of the tonsil and lateral pharyngeal wall associated with swelling in the areas of the parotid gland and angle of the mandible. In contrast, posterior parapharyngeal space abscesses result in posterior pharyngeal wall swelling.

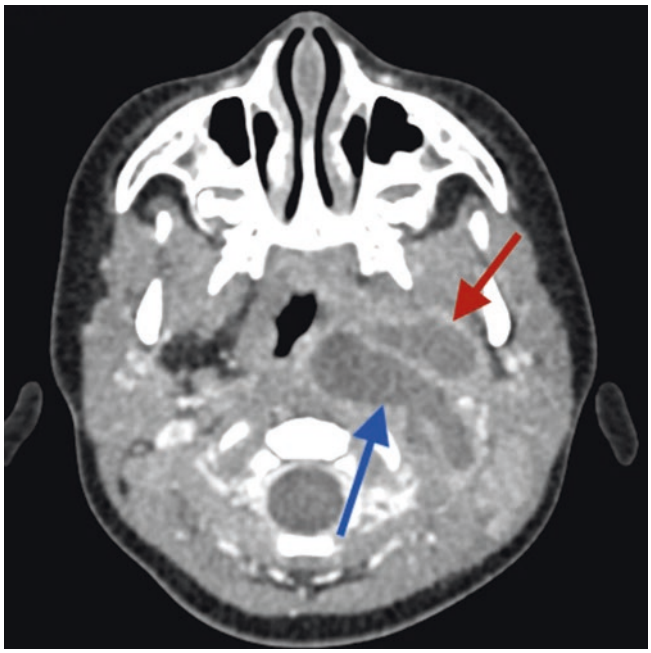


**Fig. 5.4** Shown is an axial CT scan demonstrating contiguous right-sided parapharyngeal (red arrow) and retropharyngeal abscesses (blue arrow)

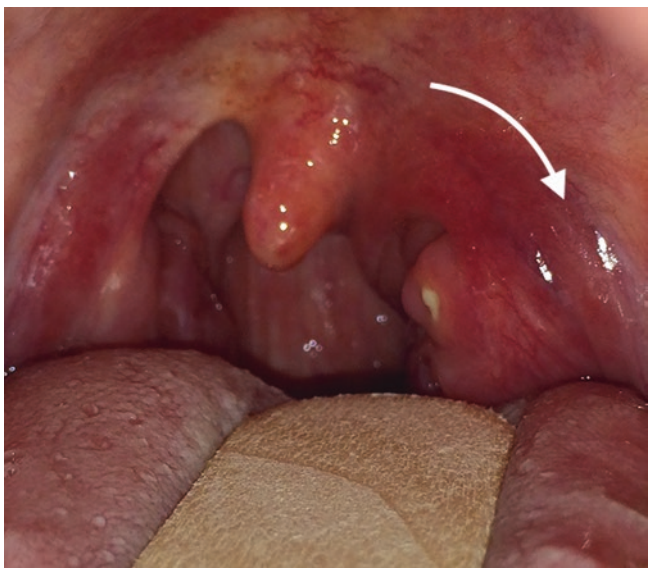


**Fig. 5.5** Cellulitis of the left anterior tonsillar pillar and soft palate in a patient with a small peritonsillar abscess (arrow)

Trismus is less frequent and, when present, less severe. Posterior parapharyngeal space abscesses are also associated with a higher incidence of sepsis due to their proximity to the carotid sheath.

Patients with RPAs often present in extremis, appearing toxic with severe respiratory distress, holding their neck in hyperextension and drooling. RPAs also cause bulging of the posterior pharyngeal wall (Fig. 5.7).

Despite the numerous clinical findings that can use to diagnose and potentially differentiate between deep neck space infections, most cases will require imaging. The imag-

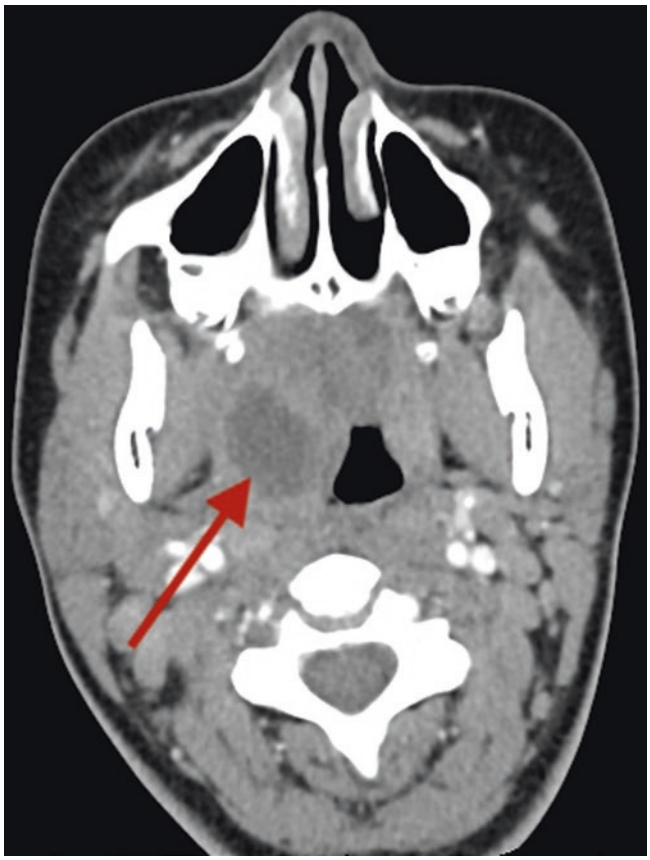


**Fig. 5.6** Shown is an axial CT scan establishing the presence of a left-sided peritonsillar abscess (arrow)

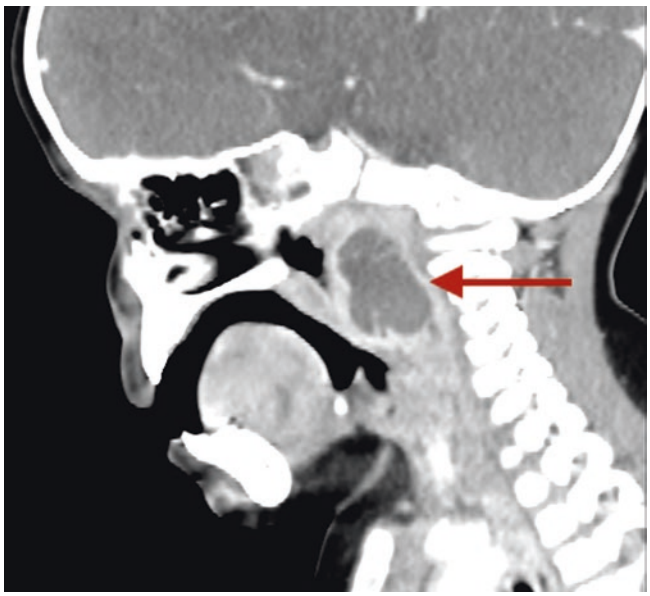


**Fig. 5.7** Shown is a sagittal CT scan showing a retropharyngeal abscess (arrow)

ing modality of choice is a contrast-enhanced CT scan of the neck. Some patients will not be able to tolerate lying supine and may require endotracheal intubation prior to the imaging procedure.

**Call Out Box 5.4**
Small, clinically mild peritonsillar abscesses, retropharyngeal abscesses, and parapharyngeal abscesses can be managed medically with close follow-up, whereas larger, more symptomatic abscesses require a surgical drainage procedure.

Needle aspiration or incision and drainage is a common method of treating abscesses in the head and neck, although intratonsillar abscesses are usually not treated surgically unless the tonsils become obstructive. Peritonsillar abscesses may be treated in a conscious patient using either needle aspiration or incision and drainage. General anesthesia is necessary for surgical drainage of other deep neck space abscesses. New evidence suggests that small PTAs, particularly those that are not associated with severe symptoms, can be treated medically, avoiding an incision and drainage procedure altogether [23]. Similarly, some small, clinically mild, parapharyngeal space abscesses [20, 24] and RPAs [25, 26] can be treated medically with close follow-up in case a surgical procedure becomes necessary due to progression of the illness [▶ Call Out Box 5.4].

Although suppurative infections of the deep neck spaces are often regarded as being more acute and in need of surgical drainage, nonsuppurative infections can be just as severe and, in some cases, more serious than deep neck space abscesses. One of these conditions is Ludwig's angina. This condition refers to a rapidly spreading cellulitic infection of the submental, sublingual, and submandibular areas, typically due to an infection originating in the teeth. The swelling of the sublingual space displaces the tongue superiorly and posteriorly. The swelling impairs speech and ability to swallow. As the infection progresses, the patency of the airway becomes compromised. On physical examination, the patient has a muffled voice and appears distressed. Trismus may prevent examination of the oropharynx. The structures of the superior neck are indurated with a marked elevation of the tongue and floor of mouth. Ludwig's angina is a surgical emergency. The treatment priority is establishing a protected airway, typically by tracheostomy. Once the airway is protected, the infection is incised and drained and the area debrided as necessary. Broad-spectrum intravenous antibiotics are used. Ideally the dental source of the infection is also addressed, but severe trismus typically prevents access during the incision and drainage procedure.

Cervical necrotizing fasciitis (CNF) is an uncommon, life-threatening infection of the head and neck associated with substantial morbidity and mortality. These infections typically arise from an existing infection of the adjacent deep neck spaces that propagates along the relatively avascular fascial planes. Because of the poor vascularity of the fascia, these infections are poorly responsive to antibiotic therapy and demand surgical debridement. Clinically and radiographically, CNF is difficult to differentiate from cellulitis or phlegmon. Symptoms typical of other pharyngeal

infections, such as sore throat, dysphagia, and odynophagia, are present; however CNF may also cause bullae, skin necrosis, subcutaneous emphysema, and pain out of proportion to the findings on examination. Secondary obstruction of lymphatic drainage can give the skin an "orange-peel" appearance [27, 28].

The classic CT scan finding of gas bubble formation within the soft tissues of the neck (Fig. 5.8) is found in 65% of CNF cases [29]. Other CT scan findings typically include the presence of diffuse edematous changes of the surrounding soft tissue and scattered areas of hypodensity that do not enhance in the presence of contrast material. Laboratory-based predictors of necrotizing fasciitis, such as the laboratory risk indicator for necrotizing fasciitis (LRINEC) score [24] and the model developed by Wall et al. [30], which are validated from other anatomic areas of the body, have not proven useful in diagnosing CNF [29]. When clinical and radiographic findings suggest the possibility that a patient has CNF, surgical exploration is necessary. If the surgical team encounters necrotic tissue that is easily pulled apart, the diagnosis of CNF is confirmed, and debridement is performed. Tissue is debrided until there is a bleeding, viable edge. Repeat visits to the operating room for additional surgeries are expected. Medical treatment involves meticulous intensive care support and the administration of long-term, broad-spectrum intravenous antibiotics. Even with prompt recognition and treatment, CNF has a mortality rate approaching 40% [31].

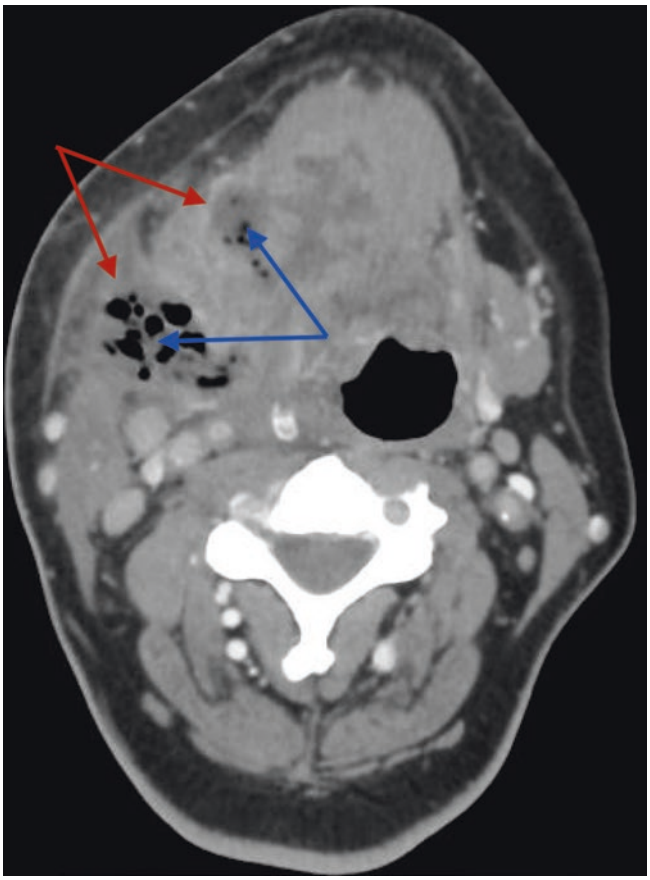


**Fig. 5.8** Shown is an axial CT scan of the neck revealing hypodense areas without peripheral enhancement (red arrows) and the abnormal presence of gas pockets (blue arrows) within the soft tissue. Surgical debridement of this area revealed necrotic tissue, confirming a diagnosis of necrotizing fasciitis

## 5.5 Imaging for Deep Space Neck Infections

The radiographic study of choice for the evaluation of a deep neck space infection is a contrast-enhanced CT scan. A CT scan provides excellent characterization of the soft tissues and bony structures. This is particularly important when there is a suspicion of an odontogenic source of infection (Fig. 5.9). Abscesses appear as areas of hypodensity with rim enhancement. Other imaging modalities, including plain radiography, ultrasonography, and magnetic resonance imaging (MRI), may be considered. Plain radiographs and ultrasonography do not provide the resolution detail that a CT scan does, but may be useful in some instances. Panoramic radiographs used to evaluate dentition may also be used to identify odontogenic sources of infection. Ultrasonography allows for the possibility of concurrent evaluation and treatment of an abscess with drainage under guidance, although the inability of ultrasound to visualize deeper structures of the neck often limits its use. MRI is rarely used in the evaluation of acute head and neck infections, but may be considered in cases where extension to the skull base, intracranial compartment, prevertebral space, or other complications, such as thrombosis of critical vessels, are suspected.

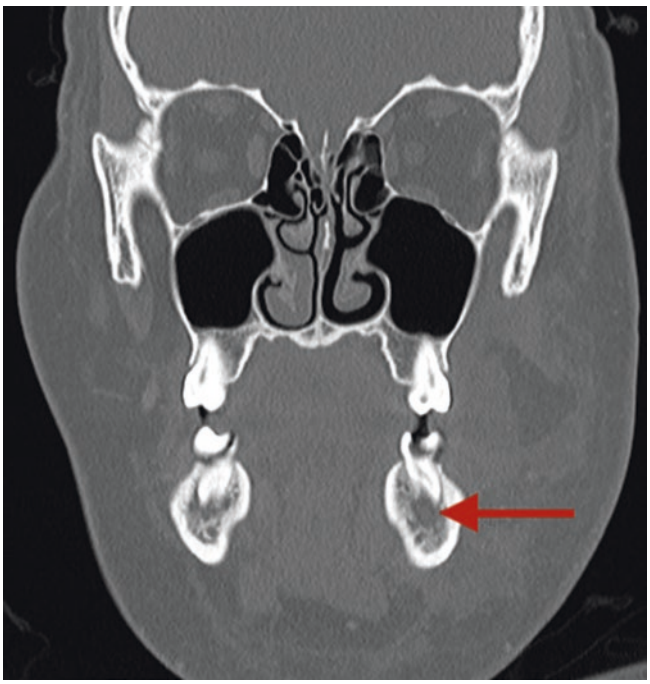


**Fig. 5.9** Shown is a coronal CT scan demonstrating a periapical lucency (arrow) in a patient with a submandibular abscess, indicating the dental source of the infection

## 5.6 Complications of Bacterial Pharyngitis and Deep Neck Space Infections

Complications of bacterial pharyngitis and deep neck space infections are uncommon, particularly if appropriate antibiotic therapy has been instituted and immediate surgical concerns have been addressed; however direct extension and invasion into surrounding structures or spaces are always a risk. Other complications include bacteremia, Lemierre's syndrome, carotid artery aneurysm/rupture, and spread along adjacent neck spaces or along fascial planes.

Lemierre's syndrome occurs when infection, usually with the anaerobic bacterium *Fusobacterium necrophorum*, extends from the pharynx or parapharyngeal space to the internal jugular vein causing an infectious thrombophlebitis. This can lead to bacteremia as portions of the infected clot break away causing septic emboli. The lungs are typically affected first. Patients with septic metastasis of infection to the lungs may develop pulmonary nodules, cavities, and abscesses. Patients may also develop septic arthritis, particularly of the knee, hip, or shoulder [32]. The diagnosis of Lemierre's syndrome is confirmed by performing a contrast-enhanced CT scan of the neck to demonstrate the presence of a thrombosed internal jugular vein. Treatment consists of intravenous antibiotics that include reliable activity against anaerobic bacteria. Some experts also recommend anticoagulation therapy. In rare instances, ligation or excision of the internal jugular vein may be necessary if the patient fails to respond to standard treatment [► Call Out Box 5.5].

Other potential complications of pharyngeal and parapharyngeal infections involving the carotid sheath are carotid artery aneurysm or rupture. These complications are extremely rare and only described in case reports. When they occur, they are life-threatening and demand immediate attention. Similar to Lemierre's syndrome, carotid artery pseudoaneurysm or rupture secondary to infection occurs due to spread of the infection from the pharynx or parapharyngeal spaces into the carotid sheath. Unlike Lemierre's syndrome, this condition tends to affect nonvascular structures in the carotid sheath, resulting in Horner syndrome and palsies of cranial nerves IX through XII. Damage to the walls of the carotid artery may produce a pulsatile neck mass on palpation, and in the case of carotid artery rupture, an expanding neck hematoma may be accompanied by a very large volume of bright red blood coming from the oropharynx. Treatment involves protecting the patient's airway and either surgical ligation or embolization to prevent circulatory collapse from blood loss.

**Call Out Box 5.5**

Lemierre's syndrome refers to infectious thrombophlebitis of the internal jugular vein that occurs as a complication of pharyngitis. It is most commonly caused by the obligate anaerobe, *Fusobacterium necrophorum*. Direct extension of the infection from the infected veins to the lungs causes a serious anaerobic bacterial pneumonia.

Spread of infection to the retropharyngeal space can lead to retropharyngeal abscesses as well as spread to other important areas of the body, such as the prevertebral space, danger space, or the mediastinum. The retropharyngeal, danger, and prevertebral spaces are bound by the skull base superiorly, and the retropharyngeal and danger spaces extend to the mediastinum, whereas the prevertebral space extends to the coccyx. Once infection reaches these spaces, there is relatively easy access to the mediastinum. The complication of mediastinal infection is rare, estimated to occur at a rate of 4.1/100,000 [33], but is always life-threatening [34, 35].

Complications specific to GAS pharyngitis include two noninfectious conditions: acute rheumatic fever (ARF) and post-streptococcal glomerulonephritis (PSGN). These entities are believed to arise from autoimmune complications secondary to the host's immune response to the GAS infection. The autoimmune sequelae seen with ARF are believed to be due to molecular mimicry, while PSGN occurs secondary to a type 3 hypersensitivity reaction.

ARF is rare within the developed world due to the availability of antibiotics; however it is still a significant cause of morbidity and mortality in developing countries [36, 37]. Untreated or multiple episodes of ARF may progress to chronic rheumatic heart disease causing lifelong complications. Acutely, patients with ARF may present with fever, arthritis, arthralgia, carditis, first-degree heart block, erythema marginatum, Sydenham chorea, or subcutaneous nodules. Inflammatory biomarkers are typically elevated. A diagnosis of ARF is made by a combination of clinical and laboratory findings as outlined by the modified Jones criteria [36].

PSGN typically occurs several weeks after GAS infection. Unlike ARF, PSGN may occur despite effective treatment of the GAS infection. Symptoms of PSGN include hematuria, edema, and hypertension although many cases present with asymptomatic microscopic hematuria alone. Acute renal failure may need to be supported temporarily with dialysis, but PSGN typically resolves with time. A small number of patients go on to develop chronic renal failure.

## 5.7 Summary

Pharyngeal infections are very common, and not often life-threatening. They are usually caused by viruses and resolve without the need for any intervention. Sepsis, muffled voice, difficulty breathing, drooling, inability to turn the head, and unilateral throat swelling on exam are not normal and demand immediate attention. Additionally, findings suggestive of an abscess on imaging warrant further evaluation and possibly surgical drainage. Failure to treat these patients in a timely manner may lead to further extension of the abscess, either within the same neck space or spread to a different neck or chest space, sepsis, invasion into surrounding

vasculature, bacteremia, Lemierre's syndrome, or even death. It is also important to recognize that immunocompromised patients are at risk for different pathogens compared to immunocompetent patients.

## 5.8 Exercises

Please refer to the supplementary information section for answers to these exercises.

1. A 21-year-old male patient presents to your office for evaluation of a sore throat. He states that his sore throat began 3 days ago and is associated with a runny nose, cough, and a hoarse voice. He is afebrile and nontoxic in appearance and does not have tender cervical lymphadenopathy, but does have tonsillar exudates. He has had two episodes of GAS pharyngitis when he was a child. What is the most appropriate next step in treatment?
   a. Manage conservatively
   b. Begin empiric treatment with antibiotics
   c. Perform a throat culture and begin empiric treatment with antibiotics
   d. Perform a throat culture and use results to guide antibiotic treatment

2. A 2-year-old male patient presents to the ED in respiratory distress. His mother states that he has complained of throat pain for several days and that his voice has sounded muffled. He also developed fevers to 39 °C, and his oral intake has decreased to the point where he has not eaten for the past days. On physical examination, he is tachypneic, has a toxic appearance, and appears tired. He is sitting forward with his neck in a position of hyperextension, and he is drooling. What is your next step in the management of this patient?
   a. Obtain an emergency CT scan of the neck
   b. Obtain blood, urine, and cerebrospinal fluid cultures; initiate antibiotic treatment
   c. Perform an airway evaluation, and establish a secure airway if needed
   d. Perform a bedside ultrasound to assess for a drainable abscess

3. A 35-year-old female presents for evaluation of a sore throat. She has had the sore throat for approximately 2 weeks, and it has been worsening during this time. Additionally, she notes that her mouth hurts. She denies voice changes and difficulty breathing and states that her pain is not any worse on one side or the other. She denies any significant past medical history or use of medications, but does reveal that she is an intravenous drug user and occasionally will share needles. On physical examination, you find a diffuse white deposit over her oral mucosa that bleeds slightly when scraped. A presumptive diagnosis of oral candidiasis (thrush) is made. In addition to starting the patient on antifungal treatment, what other tests or treatments would be prudent in this patient?
   a. Antibiotics
   b. Fungal culture
   c. HIV testing
   d. None

4. A 7-year-old female presents to the emergency department for evaluation of a sore throat and difficulty eating. For the past 5 days, she has had worsening right-sided throat pain associated with fevers, chills, and a slight muffled voice. In the ED, she is febrile to 38.8 °C, but not in any respiratory distress. She is able to swallow without significant difficulty. During your physical examination, you note some fullness and erythema of the right anterior tonsillar pillar. A CT scan shows a small collection of hypodense fluid with rim enhancement in the right peritonsillar space. Acceptable options for the management of this patient include (more than one answer may apply):
   a. Hospitalize for observation and treatment with intravenous antibiotics
   b. Discharge home on oral antibiotics with follow-up in 24 h
   c. Perform a needle aspiration now
   d. Take the patient to the operating room for an incision and drainage under general anesthesia

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# Pertussis and Pertussis Syndrome

## A Whooping Cough

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**Learning Objectives**

- Recognize the burden of pertussis disease and clinical symptoms associated with it in different age groups.
- Understand the role that adolescents and adults play in the transmission of pertussis disease and the impact that this has on the young infant population.
- Recognize the antibiotics that may be used for treatment and/or chemoprophylaxis in patients and contacts.
- Recognize the importance of immunization in the prevention and control of this disease.



## 6.1 Introduction to the Problem

- Pertussis (whooping cough) is an acute infection of the respiratory tract caused by the Gram-negative bacterium *Bordetella pertussis*. A similar pertussis syndrome is infrequently caused by *Bordetella parapertussis* and *Bordetella holmesii*. *Bordetella bronchiseptica*, one of the veterinary causes of canine kennel cough, can, on occasion, also be transmitted to humans.
- Pertussis occurs worldwide and affects persons of all ages with the highest incidence rate occurring during the first 4 months of life. Young infants with pertussis have very high rates of hospitalization for complications of the infection. The vast majority of pertussis-associated deaths occur among infants less than 6 months of age.
- Worldwide, there are an estimated 50 million cases of pertussis and 300,000 pertussis-related deaths annually.
- Pertussis is highly communicable and is easily transmitted from person to person via aerosolized respiratory droplets. Humans are the only known reservoir for *Bordetella pertussis*.
- Pertussis is a major global public health problem. Neither natural pertussis infection nor immunization results in lifelong immunity.
- Symptoms of pertussis are most severe among young infants and children, while symptoms in infected adolescents and adults may be milder, lacking an obvious "whooping component" to the cough.
- Over the last decade, an increasing amount of pertussis disease has been seen in adolescents and adults due to multiple factors including waning of vaccine-induced immunity.
- Adolescents and adults serve as major reservoirs of disease transmission to others in the community, especially to young infants who are not yet immunized because of their young age.
- Apnea may be the only symptom of disease in infants less than 6 weeks of age where the infection may also present with gagging, choking, gasping, or a brief resolved unexplained event (BRUE) instead of paroxysmal coughing and whooping.

**Call Out Box 6.1**

- Pertussis is an acute infection of the respiratory tract most commonly caused by the Gram-negative bacterium *Bordetella pertussis*.
- Illness occurs worldwide and affects persons of all ages from birth to 100 years of age.
- Pertussis is highly communicable and easily transmitted from one person to another.
- Neither natural pertussis infection nor immunization produces lifelong immunity.
- Young infants are at the greatest risk for the development of pertussis-related complications.
- The morbidity and mortality from pertussis are highest during the first 6 months of life.

- While new cases of pertussis infection occur all the time, larger outbreaks of illness typically cycle with peaks of illness occurring every 3–5 years.
- Approximately one in five cases of pertussis is complicated by bacterial pneumonia which is often secondary to a lower respiratory infection caused by *Bordetella pertussis* itself, but can also be secondary to a superinfection caused by *Staphylococcus aureus* or *Streptococcus pneumonia*. Other potential complications include seizures, encephalopathy, urinary incontinence, pneumothorax, development of an inguinal hernia, hearing loss, fractured ribs, conjunctival hemorrhage, intracranial bleeding, and other secondary infections such as otitis media [► Call Out Box 6.1].

## 6.2 Definitions

- Pertussis clinical case definition: cough greater than or equal to 14 days with one or more of the following symptoms: paroxysmal cough, inspiratory whoop, or post-tussive vomiting
- The three stages of pertussis:
  1. The illness begins with the *catarrhal stage*. The patient develops rhinorrhea without pharyngitis, low-grade fever if any fever at all; an occasional, unimpressive cough; and non-purulent conjunctivitis. This stage lasts for 10–14 days before the *paroxysmal stage* begins.
  2. The *paroxysmal stage* is marked by severe and dramatic fits of uncontrolled coughing. The patient typically coughs 10–15 times during a single expiration and then inspires forcibly causing a loud inspiratory whoop. The patient's hands, feet, and face may appear dark red or purple because episodes of coughing can be sufficiently prolonged that they result in transient hypoxemia with observable cyanosis. The whooping sound is a result of the forced inspiration against a partially closed glottis. Post-tussive gagging or vomiting is very common. The coughing fits are frequent and tend to be even worse at nighttime. Infants less than 6 weeks of age may show signs of periodic breathing or apnea without signs of coughing.

When whooping cough, caused by *Bordetella pertussis*, occurs in an unimmunized or partially immunized child, one can expect to see the characteristic hematologic findings of leukocytosis with a predominance of lymphocytes on the peripheral blood smear. It is not unusual for patients to mount total leukocyte counts of 30,000 cells/mm$^3$ or higher. Occasionally, young infants will develop peripheral leukocyte counts of 100,000 cells/mm$^3$ or more. [► Call Out Box 6.2]. The *paroxysmal stage* of pertussis may last as long as 42 days.

3. The *convalescent stage* of pertussis is marked by a gradual decrease in the frequency and severity of the coughing paroxysms. This stage may last as long as 56 days.
4. The average total illness duration of classic pertussis is 90–100 days [► Call Out Box 6.3].

- Close contact:
  1. Anyone who has had face-to-face contact or shared a confined space for 1 h or longer with an infected individual
  2. Persons who have had direct contact with respiratory, oral, or nasal secretions from a symptomatic patient through coughing, sneezing, sharing food or eating utensils, or performing mouth-to-mouth resuscitation or a medical examination of nose, mouth, or throat without the use of appropriate personal protective equipment (eg., a surgical mask)
- Antigenic components used in acellular pertussis vaccines [► Call Out Box 6.4]

**Call Out Box 6.2**

During the *paroxysmal stage* of pertussis, young infants may mount very high total leukocyte counts. The vast majority of the cells on the peripheral blood smear are lymphocytes. When the total leukocyte count exceeds 50,000 cells/mm$^3$ or more, the hematologic phenomenon is referred to as a leukemoid reaction. Any young infant who is hospitalized with an acute life-threatening illness and who is found to have a leukemoid reaction on peripheral blood smear should be evaluated for *Bordetella pertussis* infection as the finding is virtually pathognomonic for pertussis in this age group.

**Call Out Box 6.3**

- Pertussis infection is divided into three stages: catarrhal, paroxysmal, and convalescent. Total duration of illness may be as long as 4 months.
- Classic symptoms of pertussis include little or no fever, paroxysms of cough, inspiratory whooping, apnea, cyanosis, and post-tussive vomiting.
- In young infants, apnea and choking or gagging spells may be the only symptoms of the disease.
- Close contacts of an infected person, especially young infants, are at the greatest risk of acquiring the disease.

**Call Out Box 6.4**

Vaccines developed to prevent pertussis infection can be divided into two major groups. "Whole-cell" vaccines are relatively crude products derived from the entire *Bordetella pertussis* bacterium. Large-volume bacteria cultures are inactivated and the bacteria disrupted. Without using complex purification techniques, the "whole-cell" bacterial product is concentrated, stabilized, and used in the final vaccine preparation. "Acellular" pertussis vaccines are similarly derived from cultures of *Bordetella pertussis*, but the disrupted bacterial cells undergo a series of rigorous purification steps so that only the desired bacterial antigens are present in the final vaccine preparation. "Whole-cell" vaccines remain in use in many parts of the world because they are less expensive to manufacture than acellular vaccines. "Whole-cell" vaccines are also more reactogenic than acellular vaccines explaining why the majority of the world's developed nations switched to using acellular vaccines when they became available in the late 1990s.

| Component | Activity |
|---|---|
| Pertussis toxin (PT), inactivated | Promotes attachment of the organism to the respiratory epithelium, elicits lymphocytosis, inhibits phagocytic function of leukocytes |
| Filamentous hemagglutinin (FHA) | Promotes attachment of the organism to the respiratory epithelium |
| Pertactin (PRN) | Promotes attachment of the organism to the respiratory epithelium |
| Agglutinogens associated with fimbriae (FIM) | Promotes attachment of the organism to the respiratory epithelium |

## 6.3 Basic Concepts

1. Confirming the diagnosis of pertussis:
   - The gold standard for diagnosis is a culture obtained from posterior nasopharynx using a swab or by aspiration; however, specific swab types, specialized transport, and growth media are needed to enhance recovery of the organism. The specificity of culture is 100% but, depending on how the sample is collected and transported to the laboratory, has a sensitivity as low as 20%. Ideally, when culture is used, the sample should be collected within the first 3–4 weeks of cough illness. Attempts to improve the sensitivity of the culture technique once involved a form of direct inoculation onto highly selective solid culture media at the point of care. This technique, referred to as a "cough plate," was simple enough in concept. The selective media agar "plate" was stored and immediately available in the office setting. The provider would use a nasopharyngeal swab to induce a cough paroxysm and, while the patient was coughing, would hold the culture plate in front of the patient's mouth

in an attempt to inoculate the selective solid media directly from aerosolized bacterial particles. The sensitivity of the technique was highly dependent on the accuracy of the procedure. "Cough plates" are no longer used, but some clinical laboratories continue to attempt to grow *Bordetella pertussis* in culture for material collected using nasopharyngeal swabs.

- While the gold standard for diagnosis is culture, the current diagnostic tests of choice for use in all age groups are *Bordetella pertussis*-specific polymerase chain reaction (PCR) assays performed on material collected by swab or aspirate of the posterior nasopharynx. PCR testing benefits from excellent sensitivity (93.5%) and high specificity (97.1%). The turnaround time from collecting the sample to receiving the result is now typically with a day or two at most major medical centers. Optimal results are obtained when the biologic sample is collected for testing during the first 3–4 weeks of the cough illness [▶ Call Out Box 6.5].
- In general, antibody testing to document a recent pertussis infection should be avoided because it is often not possible to determine whether the presence of *Bordetella pertussis*- specific antibody is a result of prior vaccination or secondary to a recent infection. For adolescents and adults who are suspected to be coughing from pertussis, but culture or PCR-based testing was not performed in the first 3–4 weeks of the illness, serologic testing may hold some value. A single titer of IgG antibody against pertussis toxin that is greater than 125 IU/mL has been found to be highly sensitive and specific for the diagnosis of a recent pertussis infection. Keep in mind that antibodies directed against pertussis toxin are the only ones specific for *Bordetella pertussis* and that all available pertussis-containing vaccines include pertussis toxin as one of the immunizing antigens. As such, the presence of a high antibody titer directed against pertussis toxin needs to be interpreted in the context of the pertussis vaccination history.

2. The differential diagnosis of other organisms and conditions that can cause a pertussis-like illness is shown in ◘ Table 6.1. The second column lists features that are more typical for each condition that may help distinguish them from pertussis when they are present. Classic whooping cough is not a difficult diagnosis to make because the cough component of the illness and the inspiratory whooping sound are classic and unique to the condition. Pertussis infection in patients beyond the infant age group can have less typical classic features that overlap substantially with the other conditions listed in the table. The less classic, milder forms of pertussis illness with an associated prolonged cough are more difficult to tease out from the long list of other possibilities.
3. Antimicrobial therapy:
   All patients with proven or suspected pertussis should be treated with effective antibiotics to prevent or limit the spread of the disease. Antibiotics that are effective for the treatment and postexposure prevention of pertussis include those in the macrolide class (erythromycin and clarithromycin), azalide class (azithromycin), and trimethoprim-sulfamethoxazole (TMP-SMX) class.

**Call Out Box 6.5**

- *Bordetella pertussis*-specific PCR is the test of choice for the diagnosis of pertussis in all age groups. The best results are obtained within the first 3–4 weeks of the cough illness.

◘ **Table 6.1** Infections and other conditions that should be included in the differential diagnosis of pertussis syndrome

| Differential diagnosis | Possible distinguishing features |
|---|---|
| Adenoviruses | High fever, sore throat, cough, and conjunctivitis |
| Aspiration pneumonia | Fever, cough, increased work of breathing |
| Bocavirus | Lower respiratory tract findings such as rales, wheezing, and crackles are more predominant |
| *Chlamydophila pneumonia* | Fever, headache, and rales may be heard on auscultation of the chest |
| *Chlamydia trachomatis* | Staccato cough, purulent conjunctival discharge, tachypnea, rales, and wheezing |
| Human metapneumovirus | Lower respiratory tract findings such as rales, wheezing, and crackles are more predominant |
| Influenza viruses | High fevers, body aches, sore throat, cough |
| *Mycobacterium tuberculosis* | Fever, cough |
| *Mycoplasma pneumonia* | More pronounced systemic symptoms, fever, and headache; rales may be heard on auscultation of the chest; cough not typically paroxysmal |
| Parainfluenza viruses | High fever, harsh barking cough, inspiratory stridor |
| Respiratory syncytial virus (RSV) | Lower respiratory tract findings, especially wheezing, are more predominant |
| Rhinoviruses/enteroviruses | Fever, sore throat, and cough, with much more predominant nasal congestion and rhinorrhea |
| Tracheal foreign body | Choking, gagging, coughing |

- Azithromycin is the drug of choice for the treatment and postexposure prevention of pertussis in all age groups. Azithromycin is better tolerated than erythromycin. This is the only antibiotic that is recommended for use in infants less than 1 month of age for the treatment or prevention of pertussis.
- Erythromycin is considered second-line therapy for the treatment or prevention of pertussis. It is specifically not recommended for use during the first month of life because of the recognized association with the development of infantile hypertrophic pyloric stenosis. Recent data, however, suggest that the use of azithromycin during the first month of life carries a similar risk.
- Clarithromycin is also considered second-line therapy for the treatment or prevention of pertussis. It is better tolerated than erythromycin.
- For patients who are allergic to azithromycin, erythromycin, and clarithromycin, trimethoprim plus sulfamethoxazole is recommended as the alternative antibiotic.

Antibiotic chemoprophylaxis is recommended for all close contacts exposed within 21 days of onset of cough in the infected individual. The antibiotic prophylaxis regimens are the same as the pertussis treatment regimen for patients of all ages [► Call Out Box 6.6].

4. Prevention:
   - Immunization against pertussis is the single most effective means of preventing disease.
   - There are two different types of pertussis-containing vaccines: whole-cell vaccines and acellular vaccines. Licensed acellular vaccines include between one and five highly purified bacterial proteins.
   - The US pediatric pertussis immunization schedule consists of DTaP (diphtheria toxoid, tetanus toxoid, acellular pertussis vaccine, pediatric formulation) administered at 2, 4, and 6 months of age to complete the primary series, with booster doses at 18 months and 4–6 years of age. Children receive another booster at age 11 or 12 years using Tdap (tetanus toxoid, diphtheria toxoid – reduced dose, reduced dose acellular pertussis vaccine, adolescent and adult formulation) starting at 11–12 years of age. Note that DTaP and Tdap contain the same immunizing antigens but that the adolescent and adult formulation Tdap has a reduced amount of diphtheria and pertussis antigens.
   - In the United States, all adults 19 years of age and older are recommended to receive a single dose of Tdap vaccine. This is especially important for persons who have close contact with infants (e.g. older siblings, parents, grandparents, relatives, nannies, babysitters, daycare providers, and others). Pregnant women are recommended to receive Tdap vaccine during *each pregnancy*, ideally between 27 and 36 weeks of gestation in an attempt to optimize the concentrations of protective antibody transferred across the placenta from the mother to the fetus. The administration of booster doses of pertussis vaccine to the pregnant woman also improves the mother's protection against pertussis disease. Since approximately one third of young infants develop pertussis from their infected mother, this has proven an important strategy to reduce the burden of pertussis disease during early infancy.
   - All health-care workers with patient contact should be given a single dose of Tdap if they have not been vaccinated as an adult, irrespective of when they received their last dose of a tetanus toxoid-containing vaccine [► Call Out Box 6.7].

**Call Out Box 6.6**

- Antibiotics that are effective in the treatment or chemoprophylaxis of pertussis include the azalides (azithromycin), the macrolides (erythromycin, clarithromycin), and trimethoprim-sulfamethoxazole (TMP-SMX).

**Call Out Box 6.7**

- Immunization against pertussis is the single most effective means of preventing the disease.
- In the United States, in pregnant women a dose of Tdap vaccine is recommended with each pregnancy, ideally between 27 and 36 weeks of gestation.

## Case Study

### Practical Examples

**Case 1**

A 21-day-old infant presents with 3 days of coughing episodes that are so severe that he turns purple and stops breathing. His mother developed a cough illness 1 week before delivery but states that she never had a fever. The mother's paroxysms of coughing were so intense that she had post-tussive vomiting after each episode. She had not received a dose of Tdap vaccine during her pregnancy. Pertussis culture and PCR on both the mother and the infant were positive for *B. pertussis*.

**Case 2**

A 14-year-old patient presented with a 2-week history of cough paroxysms followed by inspiratory whooping and post-tussive vomiting. She states that she has a hard time catching her breath after the coughing episodes. On physical examination, she has bilateral subconjunctival hemorrhages due to the frequency and severity of her coughing episodes. The coughing episodes are worse at night. She states that she is afraid to fall asleep because she feels that she might suffocate. The patient had not yet received the adolescent booster dose of Tdap because she was ill with a "cold" each time she was seen in her

doctor's office. A nasopharyngeal swab was positive for *B. pertussis* by PCR.

**Case 3**
A 42-year-old emergency room physician has had a 4-week history of worsening paroxysmal coughing and gagging episodes. He was initially treated for an asthma exacerbation with no improvement in the cough. The coughing spells have become so severe that he developed bilateral chest pain. A chest radiograph demonstrated bilateral rib fractures. The physician has continued to work during this time; however, the frequency and severity of the coughing episodes have kept him from participating in the care of trauma patients, patients who require suturing or other procedures, and those who require an extensive amount of time for their evaluation. The physician has never received a dose of Tdap vaccine. A pediatrician colleague suggested that he be tested for pertussis. The PCR test for pertussis was negative; however, a single sample serology showed an elevated anti-pertussis toxin IgG titer of 500 IU/mL.

**Case 4**
A 65-year-old gentleman was preparing to visit his granddaughter who had just given birth to her first child. The granddaughter asked him to get a dose of Tdap vaccine before coming to see the infant, so he contacted his internist who advised him that he does not need protection against pertussis because this is only a disease that occurs in infants and children. He relays this information to his granddaughter who refuses to let him visit his great grandchild without first receiving a dose of the vaccine.



## 6.4 Exercises

Please refer to the supplementary information section for answers to these exercises.

1. What is the most common cause of pertussis?
2. True or False – Pertussis is a disease that occurs only in the infant and childhood population.
3. Which age group is at the highest risk for hospitalization, complications, and death from pertussis?
4. What is the accepted clinical definition of pertussis?
5. True or False – Natural pertussis infection and pertussis immunization as a young infant provide lifelong immunity against the disease.
6. True or False – A person with pertussis may cough for as long as 4 months.
7. True or False – The classic symptoms of pertussis include little or no fever, paroxysms of cough, inspiratory whooping, apnea, cyanosis, and post-tussive vomiting.
8. What is the test of choice for the diagnosis of pertussis in all age groups?
9. What antibiotics are effective in the treatment or chemoprophylaxis of pertussis?
10. True or False – Immunization with a pertussis-containing vaccine is the single most effective means of preventing pertussis disease.

## 6.5 Summary

Pertussis is caused by the Gram-negative bacterium *Bordetella pertussis*. It is an acute respiratory infection that occurs worldwide in persons of all ages and remains a major public health problem. Infants under 4 months of age are at the highest risk for complications, hospitalizations, and deaths from the disease with adolescents and adults serving as the major reservoirs of disease in the community. There are three stages of the disease: the *catarrhal stage*, the *paroxysmal stage*, and the *convalescent stage*. Together, symptoms can last as long as 4 months. The classic symptoms of pertussis include little to no fever, paroxysms of cough, inspiratory whooping, apnea, cyanosis, and post-tussive vomiting. Very young infants may not develop a cough illness, but develop apnea and gagging or choking instead. The diagnostic test of choice in all age groups is pertussis PCR performed on secretions collected from the posterior nasopharyngeal using a swab or aspirate. PCR results are most reliable if the test is performed during the first 3–4 weeks of the illness. Azithromycin is the antibiotic of choice for the treatment and chemoprophylaxis of pertussis disease. Immunization with a pertussis-containing vaccine is the single most effective means of preventing pertussis disease.

## Further Reading

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### Related Links to Journals, Books, and/or URLS

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www.cdc.gov/pertussis/index.html

# Laryngitis, Tracheitis, Epiglottitis, and Bronchiolitis

## Sore Throat, Change in Voice, Fever or a Wheezing Infant in Respiratory Distress

*Debra Tristram*




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**Learning Objectives**

- Explain the etiology, epidemiology, and clinical presentation of middle and lower airway infection in infants and children
- Formulate a differential diagnosis for respiratory distress in infants and children
- Describe the appropriate management of middle airway disease including laryngitis, croup, tracheitis, and epiglottitis
- Understand how viral bronchiolitis is diagnosed and treated

## 7.1 Laryngitis, Laryngotracheitis, and Laryngotracheobronchitis

The larynx and adjacent trachea are very prone to viral infections. Acute, isolated laryngitis is primarily a disease seen in older children, adolescents, and adults. In young children there is generally involvement of other adjacent structures in the upper respiratory tract and the lower respiratory tree; this condition is called acute laryngotracheitis, or croup. Acute laryngotracheitis may also extend into the lower respiratory tract presenting as acute laryngotracheobronchitis (LTB). Nearly all cases of acute croup are caused by viruses. In contrast, isolated tracheitis is rare and is more likely to be caused by a bacterium than a virus.

## 7.2 Definitions

**Laryngitis** – Laryngitis is defined as inflammation of the larynx, typically resulting in huskiness or loss of the voice, harsh breathing, dysphonia, and/or a painful cough.

**Laryngotracheitis (croup)** – Laryngotracheitis (or laryngotracheobronchitis, LTB) is an acute respiratory illness that involves infection of the larynx and the tracheobronchial tree.

**Tracheitis** – Tracheitis is defined as an acute infection or inflammation of the trachea. Bacterial tracheitis is an acute croup-like bacterial infection of the upper airway in children, with coughing and high fever, while viral tracheitis is often part of an acute viral infection that typically involves the larynx as well as the upper and lower respiratory tract.

**Epiglottitis** – Epiglottitis is an acute bacterial infection of the epiglottis and surrounding supraglottic tissues. Most cases of pediatric epiglottitis were once caused by *Haemophilus influenzae* serotype B, an infection nearly eliminated from all areas of the world where *H. influenzae* serotype B vaccination programs are in place. Currently, epiglottitis still occurs sporadically across all age groups with *Staphylococcus aureus* accounting for most disease beyond the age of 5 years.

## 7.3 Laryngitis

Acute laryngitis generally results from a viral infection that causes edema of the vocal cords, either by directly infecting the tissues or by stimulating excessive secretions that lead to inflammation. Most cases of acute laryngitis are caused by viruses (Fig. 7.1). Adenoviruses and influenza viruses are most commonly implicated, but infection with any of the common respiratory viruses can manifest as laryngitis. Acute bacterial laryngitis is rare in the era of vaccination, but one may encounter cases of acute diphtheria in unimmunized populations, particularly with growing vaccine hesitancy in the United States and Europe. When laryngitis presents as a chronic condition, an underlying viral etiology is possible, but a noninfectious etiology is far more likely. The differential diagnosis for chronic laryngitis includes trauma, allergic or chemical inflammation, tumor infiltration, and congenital anomalies.

The main clinical feature of acute laryngitis is a change in pitch or sound of the voice with associated huskiness, hoarseness, or complete aphonia. Nonspecific features of an upper respiratory infection are commonly present including nasal congestion, sore throat, and cough. Patients may complain that it hurts to speak. Viruses that cause laryngitis can also cause croup as the infection spreads to the more distal, adjacent airway structures. A more insidious presentation of laryngitis occurs following the vertical transmission of human papillomaviruses (HPV) from mother to child. The presence of a maternal infection with a low-oncogenic-risk HPV type (most commonly HPV type 6) at the time of birth

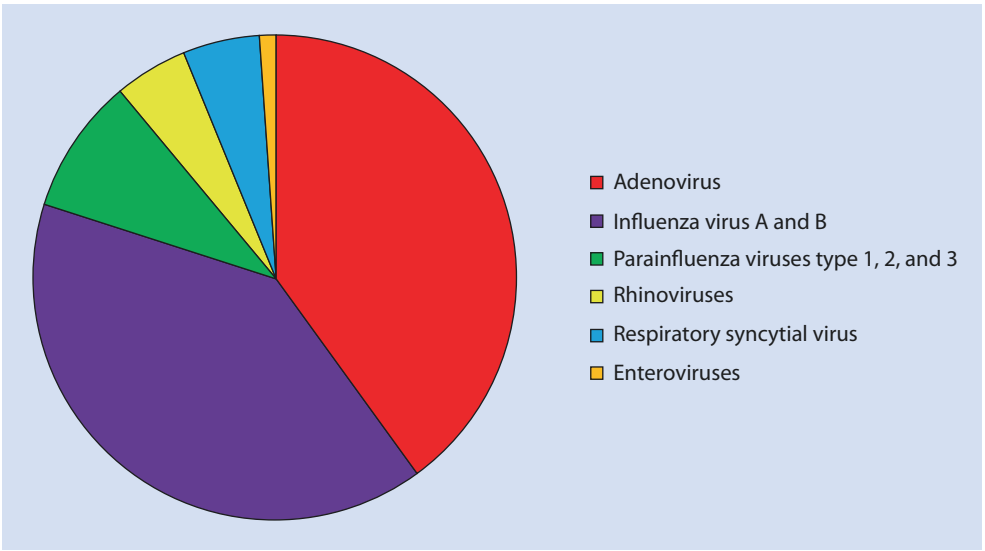



**Fig. 7.1** This pie chart shows the percentage of laryngitis cases caused by each group of common respiratory viruses

puts the newborn at risk for infection whether the mother has visible genital condylomata or not. Exposed infants may develop HPV infection in or around their vocal cords with subsequent growth of papillomas. Presenting signs and symptoms mimic viral croup, but do not completely resolve. Direct visualization using nasopharyngeal laryngoscopy is diagnostic. Surgical ablation using laser energy reduces the size of the lesions, but recurrences are expected. Recurrent respiratory papillomatosis mimics croup, and is caused by a virus, but it is a unique entity that can be very challenging to manage.

In otherwise healthy individuals, acute laryngitis is a self-limited illness lasting between 3 and 7 days. Since the vast majority of cases are due to viral infections, the use of antibiotics is not indicated. Maintenance of good hydration and resting the voice are generally sufficient therapy for acute disease. Patients should avoid "whispering" as this tends to increase trauma to vocal cords that are already irritated. Decongestant medications may be helpful if they are not too drying.

The differential diagnosis for a patient with acute vocal changes includes laryngeal edema due to trauma, particularly following toxic ingestions (e.g., lye) or inhalations, acute allergic reactions, foreign body aspiration or ingestion, and epiglottitis (▶ Box 7.1). High fever accompanied by a toxic appearance suggests an alternative diagnosis, such as epiglottitis or bacterial infection of the pharyngeal/parapharyngeal space. More insidious or chronic changes can be due to the presence of a congenital malformation, perinatally acquired respiratory papillomatosis, gastroesophageal reflux, allergic rhinitis, vocal cord nodules, or, rarely, malignancies of the larynx, vocal cords, or surrounding structures.

**Box 7.1 Differential Diagnosis of Respiratory Distress by Clinical Diagnosis**

| Clinical condition | Differential diagnosis | Helpful clues to diagnosis |
|---|---|---|
| Laryngitis | Toxic ingestion (e.g., lye) | History of exposure |
| | Toxic inhalation | History of exposure |
| | Voice overuse (e.g., singers) | History of prolonged talking or singing |
| | Acute allergic reactions | History of exposure, new food, bee sting |
| | Foreign body lodged in the larynx | History of sudden onset of choking followed by laryngitis |
| | Epiglottitis | Toxic appearance, high fever, drooling |
| | Croup | Barky cough, fever |
| Croup | Airway trauma/toxic exposures | History of exposure, smoke inhalation, other toxins |
| | Angioedema | Allergic history |
| | Foreign body aspiration | Sudden onset of choking or vomiting with choking |
| | Epiglottitis | Toxic appearance, high fever, drooling |
| | Gastroesophageal reflux | Feeding refusal, respiratory symptoms |
| | Retro- or parapharyngeal abscesses | Toxic appearance, fever, difficulty swallowing, sore throat |
| Tracheitis | Similar to croup differential | As above |
| | Diphtheria | History of prolonged endotracheal intubation followed by respiratory distress with fever |
| | | Unimmunized with or without known exposure |
| Bronchiolitis | Acute exacerbation of asthma | Personal or family history of asthma |
| | Gastroesophageal reflux | Feeding refusal, respiratory symptoms |
| | Foreign body aspiration | Sudden onset of choking or vomiting with choking |
| | Pneumonia | Fever, rales, and rhonchi with decreased breath sounds, absent or only infrequent wheezing |
| | Anaphylaxis | Allergic history, exposures |
| | Vascular rings or slings impinging the airway | Lack of accompanying symptoms of respiratory infection, chronicity |

## 7.4 Croup

When viral infections spread distally beyond the larynx to involve the trachea and the bronchi, the infection is referred to as laryngotracheitis or laryngotracheobronchitis (LTB). LTB is a more descriptive term, but "croup" is more commonly used.

Viral croup is the most common infectious cause of upper airway obstruction in young children. Infection involves the respiratory mucosa along the subglottic region. Anatomically, the subglottic diameter and circumference correlate with the age and size of the child. The smaller diameters make very young children prone to the obstructive process caused by infection-associated edema. The incidence of croup is highest among children between 3 months and 3 years of age. Outbreaks of croup typically occur in the fall and early winter just preceding the onset of RSV and influenza disease (Fig. 7.2). Parainfluenza viruses types 1, 2, and 3 account for nearly 80% of all cases (Fig. 7.3). Influenza A and B viruses can cause severe LTB and are more commonly associated with the development of secondary bacterial tracheitis and pneumonia caused by *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* [1]. Respiratory syncytial virus (RSV) and other common respiratory viruses, such as adenoviruses, rhinoviruses, human metapneumoviruses, human bocaviruses, and human coronaviruses (NL63 in particular), are less common causes of acute viral croup.

A child with croup typically presents with a prodrome of nonspecific upper respiratory symptoms preceding the onset of laryngeal symptoms for approximately 24 h. Symptoms of coryza and hoarseness are generally present early on. Progression of illness involves development of a characteristic cough that has a barking quality, like a seal. Varying degrees of inspiratory stridor become apparent, sometimes associated with tachypnea. These symptoms generally start abruptly and are typically worse at night (**see** ▶ Box 7.2). Most children with croup have low-grade fever (generally ≤101 °F) and do not appear toxic, but some of the viral causes, particularly parainfluenza virus type 3, have the potential to cause higher fever. The progression of disease is variable among children. Most gradually recover over the course of 3–7 days. Severe disease requiring endotracheal intubation is unusual, occurring in fewer than 2% of cases. Using assessment tools such as a croup score [2] may be helpful in determining the severity of the disease and to guide management in acute care settings (▶ Box 7.3).

Since the diagnosis of croup is generally made on clinical grounds, the routine use of airway or chest radiography is not indicated. If radiographs are obtained, a classic "steeple sign" may be apparent on the anterior-posterior view of the neck. The finding is due to the abnormally long area of airway narrowing that extends well below the anatomic narrowing normally seen at the level of the larynx.

At home management of croup has traditionally included the use of mist or humidified air. Despite its widespread use, no clinical benefit was noted from studies of children seen in acute care settings. In contrast, a recent Cochrane review [3] concluded that a single dose of corticosteroids should be used to treat most children with croup. Corticosteroid treatment is associated with a shorter duration of stay in the emergency department or in the hospital, if admitted, fewer hospitalizations, and fewer return visits to emergency departments. Most experts cur-

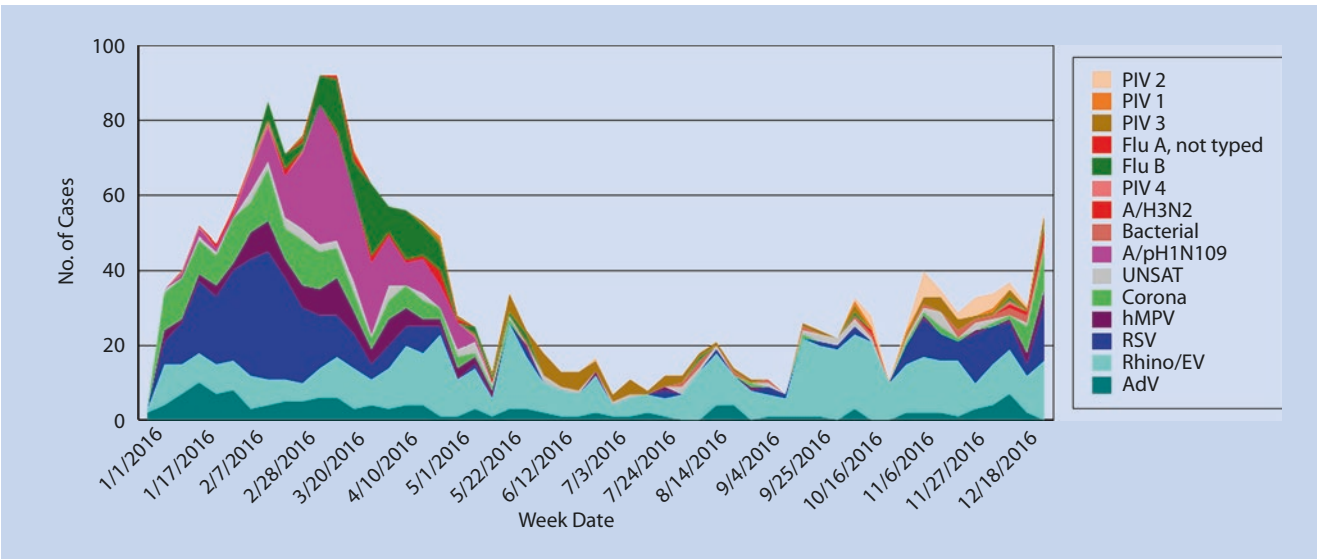



**Fig. 7.2** Respiratory viruses identified by PCR technology from patient samples submitted to Albany Medical Center's Molecular Diagnostics Laboratory during 2016. Late fall and winter seasonal patterns are seen for respiratory syncytial virus (RSV, dark blue), coronaviruses (bright green), and human metapneumovirus (hMPV, maroon). The detection of parainfluenza viruses (PIV 1, 2, and 3, tan, orange, and light brown, respectively) was also seasonal, starting earlier in the fall. The detection of adenoviruses (AdV, dark green) and rhinoviruses/enteroviruses (rhino/EV, light blue) occurred throughout the year, without clear seasonal patterns. (Figure courtesy of Albany Medical Center Virology/Molecular Diagnostics Laboratory)

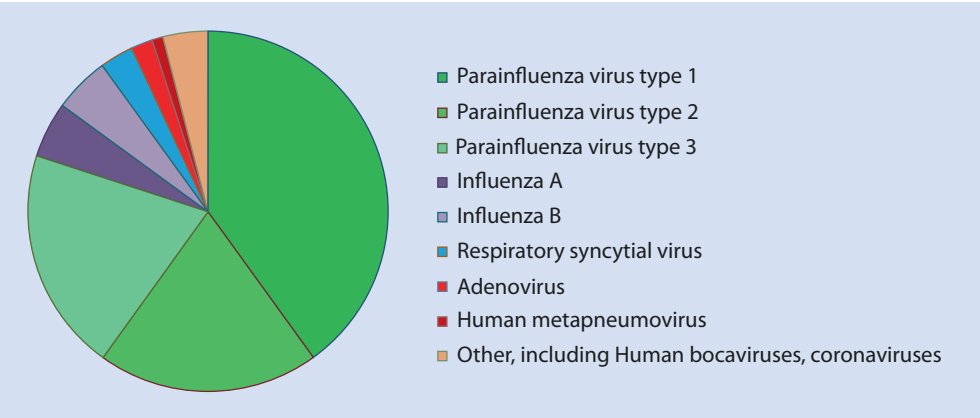



**Fig. 7.3** This pie chart shows the percentage of pediatric croup cases caused by specific respiratory viruses

**Box 7.2 Clinical Features of Croup**

- Most common in children between 3 months and 3 years of age
- Pathology located in the subglottic region
- Gradual onset with an upper respiratory prodrome
- Low-grade or absence of fever
- Nontoxic appearance
- Varying degrees of stridor from mild to severe
- Barky cough that sounds like a seal
- Cough and stridor often worse at night

**Box 7.3 Clinical Features Used to Assess Croup Severity**

| Clinical feature | Score |
|---|---|
| Level of consciousness | Normal, including sleep = 0<br>Disoriented = 5 |
| Cyanosis | None = 0<br>With agitation = 4<br>At rest = 5 |
| Stridor | None = 0<br>With agitation = 1<br>At rest = 2 |
| Air entry | Normal = 0<br>Decreased = 1<br>Markedly decreased = 2 |
| Retractions | None = 0<br>Mild = 1<br>Moderate = 2<br>Severe = 3 |

A total score of 2 or less indicates mild croup, between 3 and 7 indicates moderate croup, between 8 and 11 indicates severe croup, and 12 or higher indicates impending respiratory failure (Ref. [2])

rently recommend the use of dexamethasone which can be administered orally, intravenously, or intramuscularly. Nebulized budesonide has also been used. Nebulized racemic epinephrine is also effective at achieving temporary symptomatic improvement in children with moderate to severe croup [4]. While the treatment is safe, there may be transient side adverse effects such as pallor and tachycardia. Many institutions have developed their own algorithms for the management of pediatric croup in the acute outpatient setting. One excellent algorithm for the assessment and management of croup can be found at ► www.topalbertadoctors.org/download/252/croup_guideline.pdf (Appendix A, accessed June 27, 2017).

For children with moderate croup who fail to improve within 4–6 h after the administration of a corticosteroid, hospitalization should be considered. Children with severe croup should receive a single dose of corticosteroid and a dose of nebulized racemic epinephrine. Repeat doses of nebulized racemic epinephrine are then administered as needed in an effort to avoid the need for endotracheal intubation. Intensive care support may be needed if there is an insufficient response to repeated doses. It is important to remember that the beneficial effects of nebulized racemic epinephrine wane over 1–2 h. Close observation is necessary as the epinephrine effect declines.

Children with croup who consistently have oxygen saturations below 92% in room air should receive supplemental oxygen. Other available treatment modalities such as the use of nebulized saline, inhaled helium and oxygen mixture (heliox), and antitussive or decongestant medications are not generally recommended. Antibiotics are also not indicated unless there is a suspicion for a secondary bacterial infection. Croup, caused by influenza A or B, can be treated with oseltamivir.

The vast majority of children experiencing croup do not have complications, but a small percentage require endotracheal intubation and mechanical ventilation. Children with uncomplicated croup generally improve within 2–3 days.

The differential diagnosis for croup includes airway trauma (especially secondary to caustic agents that are swallowed or inhaled), angioedema, foreign body aspiration, tracheitis, epiglottitis, and gastroesophageal reflux (► Box 7.1). Retropharyngeal, parapharyngeal, tonsillar, or peritonsillar abscesses may present with stridor due to acute swelling. Such patients typically have high fever and appear very ill or toxic. Pharyngeal diphtheria could mimic

some of the features of croup and should be considered in the differential diagnosis if the patient is unimmunized or has been exposed.

## 7.5 Bacterial Tracheitis

Bacterial tracheitis is an invasive, exudative bacterial infection of the soft tissues of the trachea and adjacent structures. It may be difficult to differentiate clinically from viral croup, but children with bacterial tracheitis typically appear toxic, have high fevers, and are in significant respiratory distress. When bacterial tracheitis is seen, it is almost always in the setting of prior airway damage such as occurs with prolonged intubation or during an acute viral infection [1].



Organisms that cause bacterial tracheitis are generally those bacterial species that inhabit the normal upper respiratory tract, collectively referred to as oropharyngeal flora. *Staphylococcus aureus*, *Streptococcus pyogenes*, and *Streptococcus pneumoniae* are the most common causes, but Gram-negative enteric bacteria such as *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* can also cause infection of the trachea, especially in hospitalized patients. Influenza A is one of the most common predisposing viral infections, but other respiratory viruses including RSV, parainfluenza viruses, and measles have also been implicated.

Clinical features of acute bacterial tracheitis share many features with the more common viral infections in this anatomic area. Presenting symptoms may include stridor, cough, and varying degrees of respiratory distress. The infection may progress rapidly causing airway obstruction or impending respiratory failure. Signs that are concerning for impending respiratory failure include marked retractions, evidence of fatigue, listlessness, or depressed level of consciousness. In contrast to most children with viral croup, fever is almost invariably present and is generally high grade (39 °C or greater). Patients appear toxic. The severity of the clinical presentation, or acute worsening of symptoms in any patient recovering from viral croup, strongly suggests that an underlying secondary bacterial infection has intervened. Clinical features of the antecedent viral infection such as rhinorrhea, cough, and even wheezing may still be present.

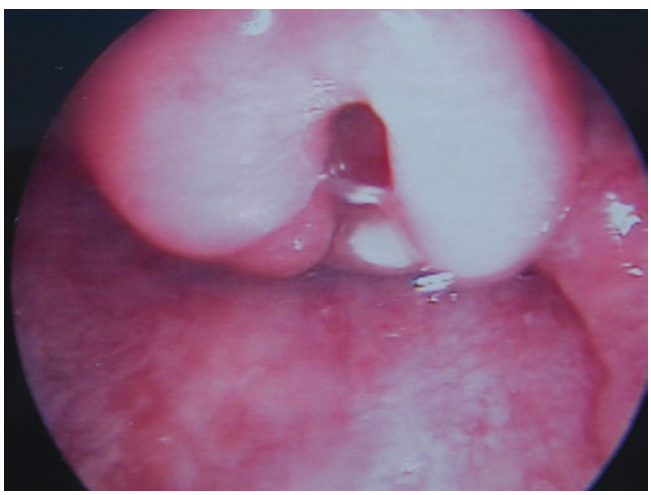
Management of bacterial tracheitis requires provision of a stable airway and the administration of broad-spectrum, empiric antibiotics directed at the group of oropharyngeal pathogens known to be the usual causative agents. Most patients require endotracheal intubation. During the procedure, samples should be collected for Gram stain and bacterial culture. Microbiologic results should be used to de-escalate the initial antibiotic regimen, if appropriate.

The differential diagnoses for acute bacterial tracheitis and acute viral laryngotracheobronchitis are similar and include foreign body aspiration, pharyngeal diphtheria, epiglottitis, and peritonsillar, parapharyngeal, and retropharyngeal abscesses (▶ Box 7.1). Final diagnosis may require direct visualization of the airway, a procedure best performed under highly controlled circumstances, by individuals experienced in quickly and efficiently establishing a secure airway under difficult circumstances, including the use of cricothyrotomy, if necessary.

## 7.6 Epiglottitis

Epiglottitis is a bacterial infection of the epiglottis and supraglottic structures that result in marked swelling of the epiglottis associated with a high risk for acute, complete, airway obstruction (◘ Fig. 7.4). Historically, epiglottitis was almost always caused by *H. influenza*e, serotype B. In the United States, infants and young children have been immunized against *H. influenza*e, serotype B, since 1990. Prior to vaccine introduction, approximately 20,000 cases of invasive disease were reported annually among children less than 5 years of age. Presently, fewer than 50 annual cases occur, almost exclusively among children who are too young to have completed the primary vaccine series, unvaccinated by parental choice, or found to have a primary humoral immune deficiency. Several other bacterial pathogens can cause acute epiglottitis but none with the proclivity once seen with *H. influenzae* serotype B. Examples of pathogens known to cause sporadic cases of epiglottitis include *H. influenzae* serotypes A and F and non-typeable strains, *Streptococcus pyogenes* (group A streptococcus) and *Staphylococcus aureus*.

Children with epiglottitis present with a sudden onset of high fever and acute respiratory distress. They are pale and anxious and appear toxic. They prefer to sit in a tripod position, leaning forward with their hands on their knees, their head in a "sniffing position," and their face in a raised position in an instinctual attempt to optimize the patency of their narrowing airway. They can develop sudden and complete airway obstruction, so they should be perturbed as little as possible. The clinical scenario is not a time to insist on performing an examination of the oropharynx, performing



◘ **Fig. 7.4** Laryngoscopic view of the inflamed and markedly swollen epiglottis of a 3-year-old child with epiglottitis. Bacterial cultures that were collected by swabbing the surface of the epiglottis immediately after the airway was secured grew *Haemophilus influenzae*, serotype B. A review of the medical history confirmed that the boy had not been immunized. (Photo courtesy of Jason Mouzakes, MD)

phlebotomy, or inserting an intravenous catheter. The child should be left undisturbed in the position of greatest comfort to them, while personnel skilled in emergency airway management assemble to prepare to secure the airway under highly controlled condition, such as the operating room. Supplemental oxygen should be offered if the child does not become agitated with its delivery. The airway must be secured as the first priority. Antibiotics are indicated and should include a second- (e.g., cefuroxime) or third- (e.g., ceftriaxone) generation cephalosporin to provide coverage for *H. influenzae*, serotype B. If the microbiology laboratory reports growth of a beta-lactamase-negative *H. influenzae*, serotype B isolate, ampicillin may be used to complete the antibiotic course. First-generation cephalosporins should not be used as they have no activity against *H. influenzae.*

Children with epiglottitis undergo endotracheal intubation for acute airway management by an experienced operator and should remain intubated until there is an air leak present around the endotracheal tube. While intubated, care must be taken to avoid accidental dislodgement of the endotracheal tube, including the use of adequate sedation, and gentle, appropriate arm and hand restraints. With antibiotic treatment, the epiglottic swelling associated with the infection gradually subsides over 3–5 days. Most children recover without any adverse effects.

**Case Study**

**Practical Examples**

A frantic mother calls the on-call physician during the night. Her 3-year-old child had a runny nose and cough yesterday but woke up a few minutes ago from coughing so hard and is now making a scary sound when he is trying to breathe in, like he cannot get any air. You ask several questions to assess the severity of his illness, which you suspect to be croup. She says he is awake and is not "blue," but he is making a whistling sound when he breathes in. His chest is "sucking inward." Based on these features, you conclude that he probably has moderate croup and would benefit from an evaluation in the local emergency department (ED). On arrival to the local ED, the boy's respiratory rate is 40 breaths per minute, and his oxygen saturation in room air is 94%. He has inspiratory stridor that worsens when he becomes agitated during the physical examination. He has some intercostal and supraclavicular retractions. A dose of dexamethasone is administered followed by a respiratory treatment with aerosolized racemic epinephrine. After the respiratory treatment is done, his symptoms are improved. His respiratory rate is now normal at 25 breaths per minute, and his oxygen saturation in room air is 98%. His retractions are improved, and stridor is absent. After 4 h of observation, his symptoms did not recur, so he is discharged home with specific guidance on reasons to return to the ED.

## 7.7 Exercises

Please refer to the supplementary information section for answers to these exercises.

Match the clinical feature with the *most* appropriate diagnosis. Each diagnosis is only used once.

| Pathogen | Characteristic finding |
|---|---|
| 1. Stridor | A. Epiglottitis |
| 2. Hoarse voice | B. Laryngitis |
| 3. Toxic appearance with high fever | C. Croup |
| 4. Unimmunized child with respiratory distress | D. Bronchiolitis |
| 5. Wheezing | E. Diphtheria |

? The optimal management of a child with moderate croup includes which of the following:

A. Mist therapy, fluids, O2, and dexamethasone
B. Fluids, O2, and dexamethasone
C. O2, dexamethasone, and antibiotics
D. Antibiotics, racemic epinephrine, and O2
E. Racemic epinephrine, O2, and mist

## 7.8 Summary

Childhood illnesses of the middle airway are very common and are caused by acute viral infections. Laryngitis is often associated with upper respiratory tract infection and can be one of the findings in patients who also have croup (LTB). Viral croup is the most common cause of acute respiratory obstruction in infants and young children leading to a substantial number of ED visits during the fall and winter seasons. Proper management includes the administration of a single dose of corticosteroids and, if necessary for more severe cases, aerosolized racemic epinephrine. Most children recover without sequelae. Acute bacterial tracheitis is rare but typically follows a primary problem that led to mechanical injury (endotracheal intubation) or friability (any acute respiratory viral infection) of the respiratory mucosa. Epiglottitis is rare in the era of vaccination against *H. influenzae* serotype B disease but should be considered in a toxic-appearing, unimmunized child with a high fever and respiratory distress.

## 7.9 Bronchiolitis

Bronchiolitis is a lower respiratory tract infection that primarily affects children under 2 years of age. It is one of the most common causes of illness and the most common reason for hospitalization in infants and young children. Most of the infants who require hospitalization have identifiable risk factors that place them at high risk for bronchiolitis, but even otherwise healthy infants and older children can develop severe infection requiring hospitalization. Some develop respiratory failure requiring mechanical ventilation. Global estimates indicate that more than 3.4 million infants require hospitalization and as many as 250,000 infants die from bronchiolitis annually. Ninety-nine percent

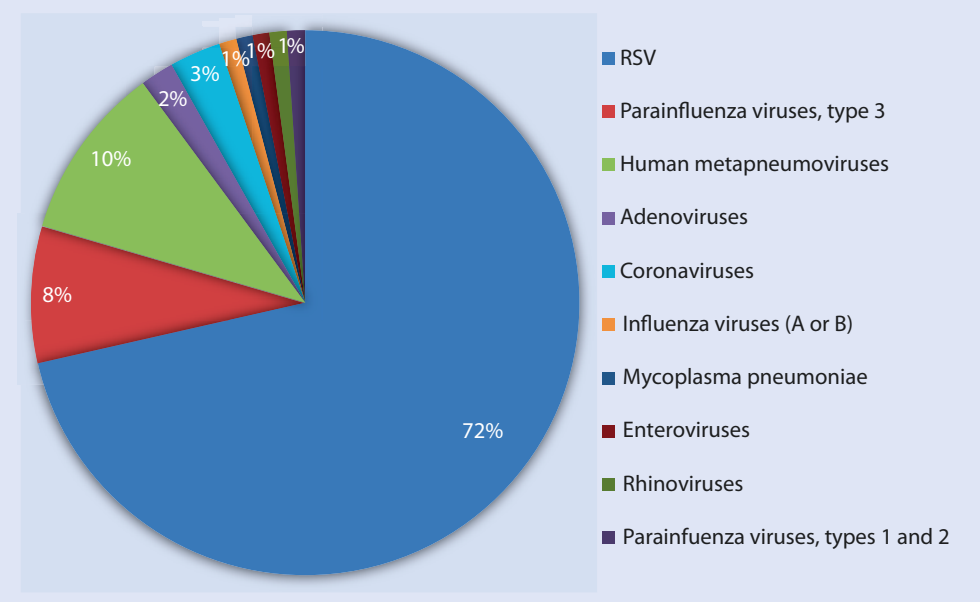



**Fig. 7.5** This pie chart shows the percentage of pediatric bronchiolitis cases caused by specific respiratory viruses



of all infant deaths from bronchiolitis occur in underdeveloped countries.

## 7.10 Definitions

Bronchiolitis: Bronchiolitis is a viral infection of the terminal bronchioles, generally preceded by infection in the upper and middle respiratory tract. The illness is characterized by wheezing, tachypnea, and respiratory distress that ranges in severity from "the happy wheezer" to respiratory failure. The term "viral bronchiolitis" is a diagnosis generally restricted to infants and very young children who present clinically with wheezing and tachypnea typically associated with other common signs of an acute viral infection of the respiratory tract including cough, nasal congestion, and rhinorrhea.Bronchiolitis is one of the most common respiratory illnesses in children worldwide [5]. Outbreaks of bronchiolitis occur annually, and while the precise timing and overall severity of each year's outbreak vary from year to year, region to region, general seasonal patterns are quite predictable in much of the world. In temperate climates, outbreaks occur during the fall and winter months as respiratory viruses circulate throughout communities. In tropical and subtropical climates, the year-round baseline of disease activity tends to be higher than seen in temperate areas, with outbreaks of disease occurring during the rainy season. Limited data suggest that desert climates are associated with substantial bronchiolitis disease activity year-round.

Bronchiolitis affects infants and young children, with a peak incidence occurring between 2 and 6 months of age. Respiratory syncytial virus (RSV) is, by far, the leading common cause of bronchiolitis, accounting for two thirds of cases. The second and third most common causes, human metapneumovirus and parainfluenza virus type 3, account for more than half of the remaining cases. All of the other common respiratory viruses have potential to cause bronchiolitis as part of their potential spectra of disease, but each contributes to only a small percentage of total cases (Fig. 7.5) [6].
Bronchiolitis develops when a viral upper respiratory tract infection progresses to the distal lower respiratory tract. The early signs and symptoms of cough, congestion, and rhinorrhea, with or without fever, persist as the infant or child begins to wheeze and exhibit varying degrees of respiratory distress. The onset of wheezing and tachypnea heralds the development of lower respiratory tract involvement. Young children are particularly prone to bronchiolitis with wheezing because smaller airways are more prone to partial or complete obstruction when they become inflamed and filled with mucous. Shifting areas of local obstruction and mucous plugging results in air trapping that can usually be appreciated on chest radiography as hyperinflation and atelectasis (Fig. 7.6) and is, at least in part, responsible for the diffuse wheezing heard on chest auscultation. Tachypnea, with respiratory rates of 100 breaths per minute or more, is not uncommon and will eventually impede the infant's ability to adequately feed. Oxygen saturation, as measured by pulse oximetry, can vary minute to minute due to shifting areas of mucous plugging and atelectasis that lead to varying degrees of ventilation to perfusion mismatch [7]. On clinical grounds, viral bronchiolitis and viral pneumonia are difficult to distinguish from one another since they represent a spectrum of lower respiratory tract illness that exist on a continuum. Accurately distinguishing between the two is not clinically important since the approach to patient management is the same.
The pathophysiology of bronchiolitis originates from infection of the cells lining the terminal bronchioles. The infection causes direct cellular damage while also stimulating local host inflammatory responses. Virus-induced inflammation results in edema, mucus production, and the recruitment of inflammatory cells. Sloughing of dead epithelial cells into the inflamed, mucous-filled airway lumen leads to obstruction of the small airways.Most infants who develop bronchi-

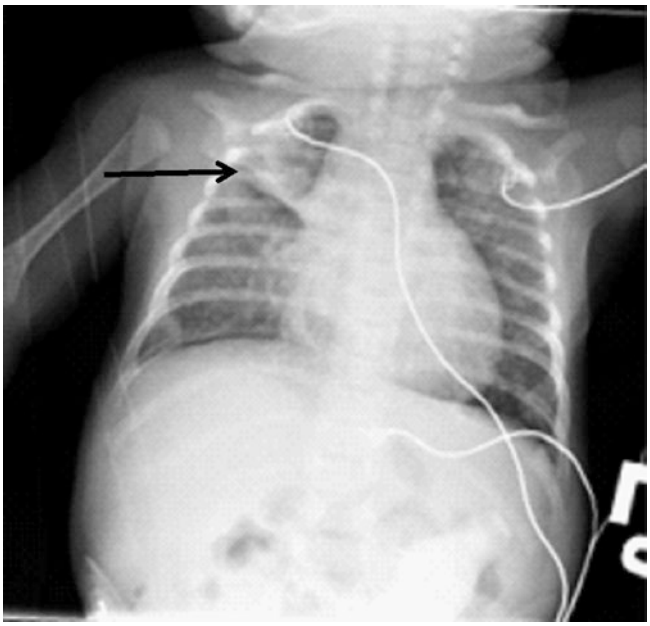


**Fig. 7.6** This chest radiograph, from a young infant with RSV bronchiolitis, demonstrates the typical radiographic features of bronchiolitis including hyperinflation, flattening of the diaphragms, and areas of atelectasis, visible here as a linear density in the right upper lung (*arrow*)

olitis will not require hospitalization. Risk factors known to be associated with more severe disease and therefore more likely to require hospitalization are well described (▶ Box 7.4) [8]. Prematurity, low birthweight, chronic lung disease, hemodynamically significant congenital heart disease, and age less than 3 months are independent risk factors for severe disease, especially when bronchiolitis is caused by RSV. Children with exposure to cigarette smoke or other air pollutants, who live in crowded households and at high altitude, attend daycare, and have preschool-aged siblings, are also at risk for more severe disease.The ability of an infant to breast- or bottle-feed is a good indication of the clinical severity of their illness and should be observed if possible. Those who cough, struggle to breathe, or sputter during feeding should be considered for hospitalization. Infants with tachypnea above 60 breaths per minute and/or oxygen saturations less than 92% should also be considered for admission. Treatment of children who are hospitalized with bronchiolitis is supportive [9, 10] (▶ Box 7.5). Supplemental oxygen should be provided to those infants who have oxygen saturations of less than 92% in room air. Oxygen saturation, as measured by pulse oximetry, can vary from minute to minute and should be measured continuously in hospitalized infants. Intravenous fluids should be administered to those infants who are unable to feed due to respiratory distress. Infants with severe hypoxemia or clinical evidence of fatigue from ongoing tachypnea should be considered for endotracheal intubation and mechanical ventilation.Prevention of bronchiolitis is challenging. The only etiologies of bronchiolitis for which vaccines are available are the influenza viruses. While the burden of influenza virus-associated disease is substantial, it accounts for only a

**Box 7.4 Risk Factors for the Development of Severe Bronchiolitis**

| Patient factors | Environmental factors | Social factors |
|---|---|---|
| Prematurity | Exposure to tobacco smoke | Older siblings |
| Low birthweight | Exposure to other air pollutants | Daycare attendance |
| Chronic lung disease, particularly bronchopulmonary dysplasia; abnormal airway anatomy | Living at an altitude higher than 2500 m (~8200 ft)[a] | Twins and other multiple births |
| Hemodynamically significant congenital heart disease, especially if associated with left-to-right shunting | Crowded household | |
| Age less than 3 months | | |
| Immunodeficiency | | |
| Down syndrome | | |
| Neurologic disease | | |
| Native American | | |

[a]Examples: Asia, Lhasa, Tibet; North America, Leadville, CO, USA; South America, Quito, Ecuador; Africa, Adi Keyh, Eritrea. The highest inhabited towns on the other three continents are below 8200 feet. Europe, Ushguli, Georgia, at 6900 feet; Australia, Perisher Village, at 5600 feet; and Antarctica, both small settlements sitting close to sea level

**Box 7.5 Treatment and Management of Acute Viral Bronchiolitis**

- Most can be managed at home with supportive care
- Hospitalize those who are unable to feed and those who are hypoxemic in room air
- Administer supplemental oxygen if needed
- Replace fluid deficits; maintain hydration
- Attempt to keep nasal passages clear, because young infants are obligate nose breathers
- Bronchodilator therapy
  - No convincing evidence to support routine use
  - A trial of aerosolized bronchodilator can be considered. If used, assess response
  - If no improvement in oxygen saturation or respiratory distress, discontinue use
  - If undesirable side effects are seen, such as excessive tachycardia or pallor, discontinue use
- Glucocorticoid therapy
  - No convincing evidence to support routine use
- Antimicrobial therapy
  - Oseltamivir can be considered for influenza virus-associated bronchiolitis
  - Secondary bacterial infections are uncommon, but when suspected antibiotics should be administered

very small percentage of bronchiolitis cases (Fig. 7.5) [8, 10, 11]. RSV bronchiolitis currently can be moderated or prevented by the provision of a monoclonal antibody, palivizumab, if administered monthly during the RSV season by IM injection. Its use, however, is restricted to very high-risk infants and does not address the greater problem of the enormous disease burden carried by otherwise healthy infants during their first 3 months of life.The prognosis of bronchiolitis is excellent. Most children recover completely within 5–7 days. Long-term studies of infants with wheezing due to bronchiolitis have shown that a substantial percentage will go on to have further episodes of reactive airway disease through early adolescence [6, 11]. A link between moderate to severe viral bronchiolitis in infancy and the development of chronic reactive airway disease, including asthma, is supported by longitudinal studies, but it remains unclear if the association is causal.The differential diagnosis of bronchiolitis includes acute exacerbation of asthma, gastroesophageal reflux, aspiration pneumonia, foreign body aspiration into the lower airway, vascular rings or slings, and, uncommonly, an acute anaphylactic reaction (▶ Box 7.1).

7

**Case Study**

**Practical Examples**

A 4-month-old previously healthy male infant born at term presents to the emergency department with respiratory distress. His parents state that he had a cold starting 2 days ago with runny nose, cough, and occasional low-grade fever. His 3-year-old sister had the same thing about a week ago, but she has recovered. They note that this morning he seemed to be breathing fast and his chest was "sucking in." He was unable to drink his bottle and had a spasm of coughing during an attempt to feed. His parents spoke with their primary care provider, and she advised an emergency department visit. The infant has received all recommended immunizations for his age. The family history is negative for reactive airway disease and other pulmonary conditions.

On physical examination, the infant appears pale. His vitals include a rectal temperature of 38 °C, a heart rate of 160 beats per minute, and a respiratory rate of 60 breaths per minute. His blood oxygen saturation is 91% in room air. He has copious nasal secretions and classic signs and symptoms of respiratory distress for his age including tachypnea, nasal flaring, intercostal retractions, and prominent inspiratory and expiratory wheezing in all lung fields. The remainder of his physical examination is unremarkable.

You suspect which of the following diagnoses?

A. Laryngotracheobronchitis (croup)
B. Epiglottitis
C. Pneumonia
D. Bronchiolitis
E. Reactive airway disease

What is most common organism that causes the above condition in young infants?

A. Respiratory syncytial virus
B. Parainfluenza virus, type 3
C. *Haemophilus influenzae*
D. *Streptococcus pneumoniae*
E. There is no infectious cause of this condition

In addition to providing supplemental oxygen, which of the following options describes the most appropriate management for this child?

A. Administer fluids, obtain a chest radiograph, and start treatment with antibiotics
B. Administer fluids and start treatment with dexamethasone
C. Administer fluids and start treatment with racemic epinephrine
D. Administer fluids and consider a trial dose of albuterol
E. Arrange for emergency endotracheal intubation

## 7.11 Summary

Bronchiolitis is an acute viral infection of the terminal bronchioles. It manifests as respiratory distress and wheezing in young children. It is the most common cause of respiratory distress requiring hospitalization in children under 5 years of age. Many respiratory viruses can cause bronchiolitis, but the most common to do so is RSV. Management consists mainly of providing symptomatic support including oxygen therapy and fluids as needed to maintain hydration. Pre-exposure passive antibody prophylaxis, palivizumab, is available to help prevent serious RSV infection in the highest-risk infants. Active vaccination against influenza is available starting at 6 months of age. Influenza viruses are the only causes of bronchiolitis for which antiviral medication is available.

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### Related Links to Journals, Books, and/or URLs

Alberta Clinical Practice Guidelines Guideline Working Group. Guidelines for the diagnosis and management of croup. www.topalbertadoctors.org/download/252/croup_guideline.pdf.

http://pediatrics.aappublications.org/content/pediatrics/early/2014/10/21/peds.2014-2742.full.pdf.

# Atypical Pneumonia

## An Adolescent with Fever, Cough and Mild Dyspnea

*Elizabeth K. Nelsen*




J. Domachowske (ed.), *Introduction to Clinical Infectious Diseases*,
https://doi.org/10.1007/978-3-319-91080-2_8

**Learning Objectives**

- List the pathogens most commonly associated with atypical pneumonia.
- Review the challenges associated with diagnosing atypical pneumonia.
- Discuss the appropriate treatment options for patients with atypical pneumonia.

## 8.1 Introduction to the Problem

The term "pneumonia" is used clinically to describe any infection of the respiratory tract that involves the alveoli. More proximal bronchioles and bronchi are also involved, and the term "bronchopneumonia" is often used synonymously. Many viruses, bacteria, fungi, and several parasites can cause pneumonia. The infection leads to inflammation of airways, alveolar sacs, and adjacent vascular structures. Independent of the underlying microbiologic cause of the infection, nearly all patients will develop fever, cough, respiratory distress, and tachypnea to some degree. The World Health Organization estimates the global incidence of childhood pneumonia from all causes at 156 million cases annually, with a greater number of children affected in underdeveloped and developing countries [1]. Taken together, the pathogens responsible for causing the vast majority of atypical pneumonia cases account for up to one-third of all cases of pneumonia globally [2]. Atypical pneumonia represents a subgroup of pneumonia that can be challenging to diagnose accurately because the presenting signs and symptoms do not necessarily mirror those seen in patients with classic pneumonia. An accurate diagnosis depends on obtaining a detailed medical history, performing a careful physical examination and carrying out a series of appropriate diagnostic studies.

## 8.2 Definitions

**Pneumonia** – Infection of the lower airways classically associated with fever, productive cough, dyspnea, and tachypnea. There may be associated pleuritic chest pain.

**Atypical pneumonia** – Infection of the lower airways that does not present with classic symptoms of pneumonia.

**Community-acquired pneumonia (CAP)** – Infection of the lower airways in a previously healthy individual that began in the outpatient setting. CAP includes both typical and atypical forms of pneumonia.

**Tachypnea** – Rapid breathing, a respiratory rate faster than expected for age. A healthy adult breathing at a rate of 20 breaths per minute or faster is tachypneic. At rest, healthy children normally breathe faster than adults. Age-specific definitions for tachypnea, as are shown in ► Call Out Box 8.1 [3].

**Dyspnea** – Difficulty breathing

**Call Out Box 8.1**

**Normal baseline respiratory rates are age dependent. Tachypnea is defined by age using the following criteria:**

- Newborn–2 months: 60 breaths per minute or higher
- 2 months–12 months: 50 breaths per minute or higher
- Age 12 months–5 years: 40 breaths per minute or higher
- 5 years–17 years: 30 breaths per minute or higher
- Adults: 20 breaths per minute or higher

## 8.3 Basic Concepts

### 8.3.1 Approach to the Diagnosis of Atypical Pneumonia

Obtaining a thorough medical history, including a detailed history of present illness, is fundamental in the evaluation of a patient who presents with symptoms consistent with any respiratory tract infection. Patients with pneumonia typically present with acute onset of fever, cough, and difficulty breathing. Patients with atypical pneumonia also frequently complain of non-pulmonary symptoms, including headache, sore throat, arthralgias, and myalgias. On physical examination, patients with atypical pneumonia are nontoxic in appearance. Vital signs may show fever, mild tachycardia, mild tachypnea, and mild hypoxemia, with oxygen saturation >90% on room air. Depending on the duration and severity of illness, some patients will have signs associated with dehydration, including tacky or dry mucous membranes. Rhinorrhea and congestion may be present. Auscultation reveals the presence of rales, often throughout all lung fields. There may also be associated wheezing and a prolonged expiratory phase. In the absence of underlying cardiopulmonary risk factors or other comorbidities, progression to more severe illness requiring hospitalization, is uncommon.

Chest radiographs are sometimes performed on patients with suspected pneumonia, especially if the illness is moderate to severe or the clinical diagnosis is uncertain. Radiographic findings vary widely. The most common finding on chest radiograph, diffuse interstitial infiltrates (◘ Fig. 8.1), may be associated with lobar or segmental consolidation, atelectasis, and/or hilar adenopathy. Identified radiographic abnormalities often appear more impressive than expected based on the patient's presentation.

The practice of ordering a routine laboratory evaluation for the patient with atypical pneumonia is not routinely recommended because most of the available tests lack sensitivity and specificity, and the recommended empiric antibiotic therapy is designed to cover the likely suspects. Results from commonly performed laboratory tests, including a complete blood count and basic metabolic panel, are not helpful in making or confirming a microbiologic diagnosis. Similarly, requesting cultures from nasopharyngeal swabs or sputum collected from the patient is not routinely recommended

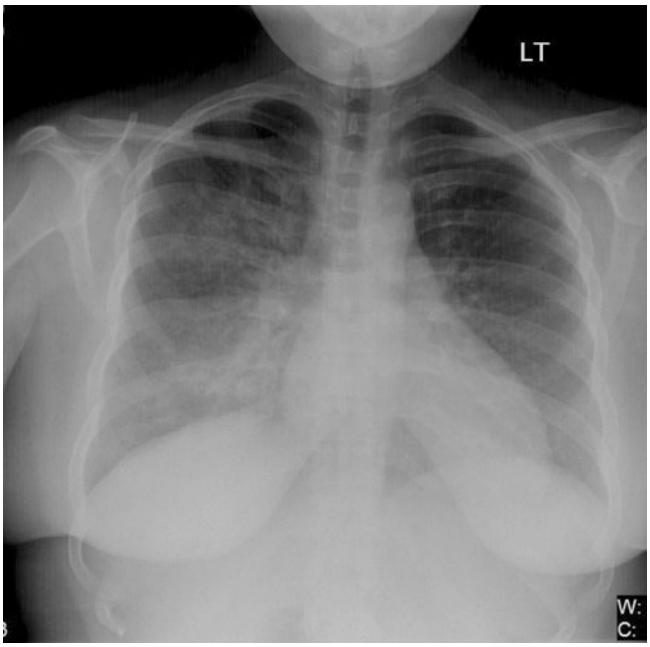


**Fig. 8.1** Chest radiograph showing bilateral diffuse interstitial infiltrates characteristic of atypical pneumonia

because most of the etiologic agents of atypical pneumonia require specialized microbiologic techniques and prolonged incubation periods before growth becomes evident. Serologic (antibody) testing can be considered, but optimal interpretation requires that samples be taken during the acute infection and again during convalescence, 2–4 weeks later. The immunoglobulin G titers obtained from the two points are then compared. For most pathogens, a fourfold rise between the acute and convalescent titer is considered a positive result. Immunoglobulin M assays for the agents of atypical pneumonia, when available, lack sufficient sensitivity and specificity to justify requesting them on a routine basis. Pathogen-specific polymerase chain reaction (PCR) testing of respiratory samples collected using nasopharyngeal swabs is becoming more widely available. Results of PCR testing may be reported on the same day if the testing is performed on site. The sensitivity and specificity of PCR is typically high, but there is variability among the commercially available test kits. Diagnostic PCR, depending on the assay used, may be limited by its high cost and need for specialized equipment. As nucleic acid-based point-of-care testing becomes more widely available and costs decrease, PCR diagnostics will be more appealing to use on a routine basis [4].

### 8.3.1.1 Differential Diagnosis of Atypical Pneumonia

Cough and respiratory distress are prominent symptoms seen in patients with community-acquired pneumonia irrespective of the underlying microbiologic diagnosis, making it impossible to determine the agent of the infection by history alone [5]. By considering age- and patient-related factors in combination with findings on physical examination, it is usually possible to narrow the list of agents that are most likely responsible for the patient's respiratory infection. Noninfectious etiologies should also be included routinely in the differential diagnosis of cough and respiratory distress. In infants, anatomical abnormalities such as tracheoesophageal fistula, vascular rings, and congenital heart disease should be considered. While the presence of cough, respiratory distress, and wheezing suggests the possibility of atypical pneumonia, the triad is also very common during respiratory viral infections and exacerbations of asthma at any age.

### 8.3.1.2 Etiologies of Atypical Pneumonia [► Call Out Box 8.2]

#### *Mycoplasma pneumoniae*

*Mycoplasma pneumoniae* is the most common and is considered the most classic cause of atypical pneumonia. Transmission occurs from person to person via respiratory droplets. The pathogen is known to express several virulence factors allowing it to gain entry into the lung. *M. pneumonia*, unlike most prokaryotes, does not have a cell wall. As such, antibiotics that target cell wall biosynthesis (penicillins, cephalosporins, vancomycin) are useless when considering available treatment options. As the bacteria replicate, they incite a robust inflammatory response leading to airway dysfunction [6]. *M. pneumoniae* infection is common among school-age children, military recruits, and college students living in dormitories.

Most patients with pneumonia caused by *M. pneumoniae* will have cough, pharyngitis, and rhinorrhea. Wheezing and dyspnea may or may not be present. A small number of patients will experience severe ear pain and on examination will have bullous myringitis. Extrapulmonary manifestations may also be present [7] [► Call Out Box 8.3]. Despite its prominent role as the most common etiologic agent of atypical pneumonia, the majority of disease caused by *M. pneumoniae* is localized to the upper respiratory tract.

*M. pneumoniae*-specific PCR testing of sputum or nasopharyngeal samples provide the greatest sensitivity and specificity among available diagnostic tests. Prolonged carriage of *M. pneumoniae* is well described, so limiting testing to the acute phase of the infection increases the likelihood that a positive test result is indicative of an active infection in need of treatment. Serologic testing for *M. pneumoniae* is also available, but low sensitivity and specificity limit their utility.

**Call Out Box 8.2**
**The five causes of atypical pneumonia:**
- *Mycoplasma pneumoniae*
- *Chlamydophila pneumoniae*
- *Chlamydophila psittaci*
- *Legionella pneumophila*
- *Bordetella pertussis*

**Call Out Box 8.3 Extrapulmonary manifestations of *Mycoplasma pneumoniae* infection**

| Body system | Manifestations |
|---|---|
| Dermatologic | Pink-red blanching macular rash, urticaria, erythema nodosum, Stevens-Johnson syndrome |
| Central nervous system | Aseptic meningitis, encephalitis, acute cerebellar ataxia |
| Cardiovascular | Pericarditis, myocarditis |
| Gastrointestinal | Pancreatitis, hepatitis |
| Musculoskeletal | Polyarthritis |
| Hematologic | Autoimmune hemolytic anemia |

**Call Out Box 8.4 Treatment options for atypical pneumonia**

| Organism | Treatment options (antibiotic of choice in **bold**) |
|---|---|
| *Mycoplasma pneumoniae* | **Azithromycin**, clarithromycin, erythromycin<br>Doxycycline, tetracycline<br>Levofloxacin |
| *Chlamydophila pneumoniae*<br>*Chlamydia psittaci* | **Azithromycin**, clarithromycin, erythromycin<br>Doxycycline, tetracycline<br>**Azithromycin**, clarithromycin, erythromycin<br>Doxycycline, tetracycline |
| *Legionella pneumophila* | **Levofloxacin**<br>Azithromycin |
| *Bordetella pertussis* | **Azithromycin**, clarithromycin, erythromycin<br>Trimethoprim + sulfamethoxazole |

Refs. [10, 12, 13]

8

When serologic testing is performed, obtaining samples during both the acute illness and during convalescence 2–4 weeks later is preferred. A fourfold rise in either *M. pneumoniae*-specific immunoglobulin M or immunoglobulin G over a 4-week period is considered a positive result. *M. pneumoniae* culture is not recommended since it is challenging to perform and requires a prolonged incubation period. The organism requires specialized media to grow, and when it does grow the bacteria colonies need to be visualized microscopically to confirm their presence [4]. Before *M. pneumoniae*-specific testing was available, providers would request testing for the presence of cold agglutinins in serum. Cold agglutinins are antibodies that cause erythrocytes to agglutinate (clump together) at cold temperatures. The test is now typically requested only by a hematologist who is evaluating a patient for a rare form of autoimmune hemolytic anemia, but transient production of cold agglutinins is also known to occur in more than half of individuals with *M. pneumoniae* infection. The test is no longer recommended during the diagnostic evaluation of a patient with atypical pneumonia because of its lack of sensitivity and specificity. More precise testing, usually in the form of PCR, is preferred.

The preferred treatment option for atypical pneumonia caused by *M. pneumoniae* is azithromycin, although other macrolide antibiotics are also effective. Treatment alternatives include tetracycline, doxycycline, and levofloxacin [► Call Out Box 8.4] [8]. Tetracycline and doxycycline should generally be avoided when treating children under the age of 8 years because they can cause staining of the permanent teeth.

### *Chlamydophila pneumoniae*

*Chlamydophila pneumoniae* (also known as *Chlamydia pneumoniae*) is another etiologic agent to consider in patients with atypical pneumonia. The organism is an obligate intracellular gram-negative bacterium. Its life cycle is unique among bacteria, as it exists in two forms. The elementary bodies (EB) are the infectious form of the organism but are metabolically inactive. They bind to the epithelial cell surface and enter via endocytosis. Once inside the cell, the EB transform into reticulate bodies (RB). The RB use energy (ATP) inside the cell to replicate via binary fission. After 48–72 h inside the cell, the RB reorganize into EB. The new EB leave the cell either by induction of apoptosis and cell lysis or reverse endocytosis [9]. Neither the EB nor RB forms have a cell wall. Infection spreads via droplet transmission with an incubation period of approximately 3–4 weeks.

Symptoms associated with infection by *C. pneumoniae* are similar to those caused by *M. pneumoniae*, but the cough may come in paroxysms and last for several weeks, thereby resembling pertussis (whooping cough). Even in patients who are minimally symptomatic the chest radiograph shows bilateral ground-glass opacities with or without the presence of nodular changes in the interstitium.

Diagnosis by laboratory testing should be made serologically, as culture is difficult and PCR may not be accurate due to prolonged asymptomatic shedding [10]. When performing serologic testing, the microimmunofluorescence (MIF) technique is recommended. A *C. pneumonia*-specific IgM of 1:16 or higher is considered positive. Alternatively, an observed fourfold increase in paired IgG titers obtained during the acute illness and again during convalescence can be used to confirm the diagnosis. Treatment recommendations are summarized in the ► Call Out Box 8.4. Azithromycin or one of the other macrolide class antibiotics is preferred.

### *Chlamydophila psittaci*

*Chlamydophila psittaci* (also known as *Chlamydia psittaci)* is an uncommon cause of atypical pneumonia. The natural reservoir for this bacteria include birds of the Psittacidae

family (parrots, macaws, and parakeets), and infection with this organism is also sometimes referred to as "parrot fever" or "psittacosis." Psittacosis should be included on the differential diagnosis in any patient with pneumonia who has had contact with psittacine birds. Person-to-person transmission is very rare. Infection occurs from either direct contact with the organism (handling of bird excrement) or through inhalation of aerosols from a sick or dead bird. The incubation period between exposure and illness ranges from 5 to 19 days.

Patients with psittacosis present with acute onset of respiratory symptoms. Other signs and symptoms include headache, epistaxis, splenomegaly, or Horder's spots, which is a red macular rash localized primarily to the face. If a complete blood count is obtained, it may reveal moderate leukopenia.

Diagnosis is best confirmed using serologic testing. As for infection caused by *C. pneumonia*, MIF is the preferred testing method. Results are considered positive if a fourfold increase in *C. psittaci*-specific IgG titers is observed from paired sera collected during the acute and convalescent phases of the infection, typically separated by 3–4 weeks [10]. Treatment options for atypical pneumonia caused by *C. psittaci* are the same as listed for *C. pneumoniae* [► Call Out Box 8.4].

### *Legionella pneumophila*

*Legionella pneumophila* is another well-appreciated cause of atypical pneumonia. While sporadic cases do occur, this pathogen becomes the number one suspect when a cluster or outbreak of atypical pneumonia is identified among a group of individuals who may have a common source of exposure. Infection from *L. pneumophila* is more prevalent among adults over age 50 years and has nearly a 2:1 male predominance. Children and adults who are immunosuppressed and adults with underlying cardiopulmonary disease or a long-standing history of cigarette smoking are more susceptible to infection. The pathogen is a small bacterium lacking a cell wall. *Legionella* species thrive in a variety of aquatic systems, including central air-conditioning systems, cooling towers, hot tubs, and ponds. Transmission occurs via inhalation of aerosolized droplets containing the organism. The incubation ranges between 2 and 19 days [11].

Infection with *L. pneumophila* can cause one of two different syndromes. Pontiac fever is a self-limited illness that presents with fever and myalgias but no respiratory symptoms. The more common syndrome associated with infection with *L. pneumophila* is Legionnaires' disease, which is also referred to as legionellosis. *L. pneumophila* was discovered during a long and nearly failed investigation of an outbreak during an American Legion convention in Philadelphia. Symptoms of Legionnaires' disease include fever, cough, and respiratory distress. Extrapulmonary symptoms including nausea, vomiting, diarrhea, headache, and mental status changes are also quite common. The overall mortality of this illness is approximately 10% but can be substantially higher during outbreaks among those with comorbidities and among those with a hospital-acquired infection [11]. Unlike other causes of atypical pneumonia, laboratory testing is very helpful in making the diagnosis. *L. pneumophila* can be cultured from sputum, induced sputum, endotracheal aspirates, or lower respiratory samples collected during bronchoscopy. The same sample(s) can be stained for the presence of the organism using a fluorescein-tagged anti-*Legionella* antibody. While this direct microscopy test lacks sensitivity, it is highly specific. If present in the respiratory secretions, the bacteria grow well on selective media with visible colonies appearing within 2–5 days.

Rapid testing for legionellosis is also available by testing the patient's urine for the presence of an antigen specific to *L. pneumophila* type 1. *L. pneumophila* type 1 is the most common serotype to cause pneumonia, but other serotypes (and other *Legionella* species) also contribute to the overall disease burden, so a negative urine antigen test does not rule out legionellosis. When used, antigen can be detected in the urine within a few days of illness onset [4]. If an outbreak is suspected, alerting the appropriate public health officials is prudent.

The antibiotic of choice for the treatment of legionellosis is levofloxacin. Other options include macrolide class antibiotics, tetracycline, and doxycycline [► Call Out Box 8.4].

### *Bordetella pertussis*

*Bordetella pertussis* causes whooping cough. The syndrome is classic and well described in a separate chapter, but up to 25% of hospitalized infants with whooping cough also develop atypical pneumonia as part of their illness. The pathogen is a gram-negative rod whose effects are mediated through the release of several virulence factors including toxins that attach to and paralyze the cilia of respiratory epithelial cells. The incubation period for *B. pertussis* ranges between 4 and 21 days. Classic whooping cough progresses through three very distinct phases of illness. The catarrhal phase is associated with low-grade fever and upper respiratory tract symptoms, which may include an unimpressive cough that lasts 7–10 days. The paroxysmal phase begins abruptly with impressive paroxysms or "fits" of coughing. Young infants can develop cyanosis during their more prolonged coughing spells. During brief periods between coughing, the patient struggles to catch their breath and will inhale deeply and quickly. This effort results in a loud, characteristic inspiratory whoop that gives pertussis infection its common name. At the end of each coughing spell, there is often post-tussive gagging or vomiting. The paroxysmal stage of pertussis continues for up to 6 weeks before the violent coughing spells begin to subside. The third phase of pertussis can last for several months. During the convalescent phase, a more typical cough persist without the associated paroxysms. Atypical pneumonia can be seen as a complication of classic pertussis. Since the signs and symptoms of whooping cough are so dramatic, the cause of the associated atypical pneumonia is not usually questioned.

The diagnosis of pertussis is confirmed by performing a *B. pertussis*-specific PCR assay on a respiratory sample collected from the nasopharynx during the paroxysmal stage of infection. Other available diagnostic tests include direct fluorescent antibody (DFA) testing, culture, and serology. PCR is the preferred testing method during the first 3 weeks of the illness because it has a much higher sensitivity and specificity than any of the other testing methods [4].

Pertussis is treated with antibiotics if the diagnosis is suspected or confirmed during the first 3 weeks of the illness. Antibiotic therapy does not impact the natural history of the cough illness associated with pertussis. The purpose of the treatment is to render the patient noncontagious. If the patient has already been symptomatic for more than 3 weeks, antibiotics are not necessary because the period of contagion has passed. Household and other close contacts should also receive antibiotics to prevent secondary cases. The antibiotic of choice for treatment and for prophylaxis is azithromycin. Other macrolide class antibiotics are also acceptable. Patients who are allergic to or cannot otherwise tolerate macrolide antibiotics can be treated with trimethoprim plus sulfamethoxazole, although efficacy of that regimen is not clearly established ► Call Out Box 8.4.

## Case Study

8

### Practical Examples

A 16-year-old female presents with a 3-day history of fever and cough. She is otherwise healthy and is fully vaccinated. Her cough is nonproductive. She denies abdominal pain, nausea, or vomiting. She had two episodes of diarrhea earlier in the day. She complains of muscle aches but denies joint pain, and she has not noticed any rashes. She has no sick contacts at home. She states that some of her high school friends have had similar symptoms recently. Review of systems reveals headache, rhinorrhea, and a sensation of tightness in her chest when breathing. On physical examination, she is well-appearing and in no acute distress. Her vital signs include a temperature of 38.6 °C and a respiratory rate of 25 breaths per minute. She has clear rhinorrhea and an injected posterior pharynx without exudates. Her neck is supple. She has several palpable lymph nodes present along the anterior cervical chain. The lymph nodes are small, minimally tender, and mobile. Her cardiac examination is normal. Lung auscultation reveals good aeration bilaterally with no areas of diminished breath sounds. She has diffuse wheezing present with a slightly prolonged expiratory phase. She also has a faint, pink macular rash on her trunk and arms that blanches with pressure. A chest radiograph shows bilateral dense opacities in both lower lung fields. Based on her clinical and radiographic findings, she is diagnosed with pneumonia, most likely secondary to *M. pneumoniae* and is prescribed a 5-day course of azithromycin. She completes her antibiotics as prescribed, and she has an uneventful recovery.

A 56-year-old male hospitalized in the intensive care unit after sustaining a myocardial infarction and undergoing coronary artery bypass grafting develops respiratory distress 6 days into his hospitalization. His symptoms include fever as high as 39 °C, productive cough, muscle aches, and diarrhea. On lung auscultation, he has diminished air entry at the bases and diffuse crackles. His condition rapidly deteriorates, requiring intubation and mechanical ventilation. While he is being worked up for the cause of his respiratory distress, two other patients in the intensive care unit develop similar respiratory symptoms. An astute clinician includes Legionnaires' disease as part of the differential diagnosis for all three patients. Urinary antigen testing for *Legionella* is positive in all three patients. All three patients are treated with levofloxacin. A cluster investigation is initiated by the local health department and the hospital infection control team, and *L. pneumophila* is cultured from water taken from the hospital's cooling towers. The cooling towers are disinfected and quality control measures reviewed to prevent the problem from recurring. Repeat sampling of water from the cooling towers were culture negative for the presence of *L. pneumophila*.

A 4-month-old infant presents to the pediatric emergency department with respiratory distress. She has had low-grade fevers not exceeding 38.3 °C, rhinorrhea, and cough for 7 days. Her parents brought her to the emergency department because she is having a hard time breathing. She has had multiple episodes of post-tussive emesis. She was born at term after an uneventful pregnancy. The infant has been growing and developing well. She has not been immunized because her parents are hesitant to allow them to be given. The infant's 6-year-old sister is also unimmunized. She has had a chronic cough that started more than 3 weeks prior to the infant's illness. The baby's parents describe the cough as harsh and nonproductive. Sometimes the coughing lasts so long that the baby turns blue. Examination of the 4-month-old reveals an ill-appearing infant. Vital signs show a heart rate of 180 beats per minute, a blood pressure of 70/30, and a respiratory rate of 70 breaths per minute. The anterior fontanelle is sunken, and her mucous membranes are dry. There is clear rhinorrhea present. Auscultation of the heart reveals tachycardia but normal rhythm without murmurs, rubs, or gallops. Lung auscultation reveals fair air entry bilaterally without areas of diminished breath sounds, wheezes, rales, or rhonchi. Capillary refill is 3–4 seconds. While completing the examination, the infant has a 10-second period of apnea following a bout of coughing. A decision is made to hospitalize the infant for further management. A chest radiograph done at the time of hospitalization shows bilaterally patchy infiltrates. The infant has more frequent and more prolonged periods of apnea, and the decision is made to support her respiratory status with mechanical ventilation. A PCR assay performed on a sample collected using a nasopharyngeal swab is positive for *B. pertussis*. The infant, the older sister, the parents, and the healthcare workers are all treated with a 5-day course of azithromycin.

## 8.4 Exercise

Please refer to the supplementary information section for answers to these exercises.

Match the descriptions listed in the second column to those listed in the first column.

| Pathogen | Characteristic finding |
|---|---|
| 1. Pneumonia | A. A self-limited illness identified by fever and myalgias that is caused by *Legionella pneumophila* |
| 2. Atypical pneumonia | B. Temporary cessation of breathing that is common in infants infected with *Bordetella pertussis* |
| 3. Walking pneumonia | C. Most accurate method for diagnosing pertussis |
| 4. Psittacosis | D. A rapid diagnostic test available for the most common serotype of *Legionella pneumophila* |
| 5. Pontiac fever | E. Commonly seen during infection with *Mycoplasma pneumoniae* |
| 6. Legionnaires' disease | F. Inflammation of lung tissue caused by a bacterial infection that does not present with classic signs and symptoms of pneumonia |
| 7. Apnea | G. An alternative name for a lower respiratory tract infection caused by *Mycoplasma pneumoniae* |
| 8. Urine antigen testing | H. An illness caused by bacteria present in water from cooling towers typically associated with clusters or outbreaks of infection |
| 9. Nasopharyngeal swab PCR testing | I. Inflammation of lung tissue secondary to infection from bacteria, viruses, fungi, or parasites |
| 10. Extrapulmonary symptoms | J. A type of lower respiratory infection that can be transmitted to humans from parrots, macaws, and parakeets |

## 8.5 Summary

There are five different pathogens known to cause atypical pneumonia. The key to ascertain the most likely microbiologic diagnosis is in obtaining a careful history and conducting a thorough physical examination. The results of most laboratory tests and finding on chest radiographs offer little help in confirming the etiologic agent. Pathogen-specific testing using serology, PCR, and/or antigen-based assays are available and can be requested. Azithromycin is used empirically for the treatment of most cases of atypical pneumonia; however, levofloxacin is the drug of choice for pneumonia known to be caused by *Legionella pneumophila*.

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**Related Links to Journals, Books, and/or URLs**

Atypical pneumonia: https://radiopaedia.org/articles/atypical-pneumonia.

*Mycoplasma pneumoniae* infection: https://www.cdc.gov/pneumonia/atypical/mycoplasma/index.html.

*Chlamydia pneumoniae* infection: https://www.cdc.gov/pneumonia/atypical/cpneumoniae/index.html.

Psittacosis: https://www.cdc.gov/pneumonia/atypical/psittacosis.html.

*Legionella* (Legionnaires' disease and Pontiac Fever): https://www.cdc.gov/legionella/index.html.

This is how Legionnaires' Disease got its name: http://time.com/3994453/legionnaires-disease-name-history-1976/.

Pertussis: https://www.cdc.gov/pertussis/clinical/index.html.

# Fungal Pneumonia

## Fever and Dry Cough After Visiting or Living in an Endemic Area

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**Learning Objectives**

- Identify the common causes of pulmonary fungal infections.
- Apply knowledge to a case to determine risk factors for fungal pneumonia.
- Plan appropriate empiric therapy for the common causes of fungal pneumonia that incorporates assessment of potential interactions and complications of antifungal therapies.

## 9.1 Introduction to the Problem [▶ Call Out Box 9.1]

Fungi and their spores are ubiquitous, yet invasive pulmonary fungal disease is a rare clinical problem. Except for limited nodular disease caused by some dimorphic fungi, infection that involves the distal airways is nearly always due to a defect in airway clearance or a deficiency or dysfunction in the immune system. Since fungal pneumonia most often occurs in the context of an immune deficiency, prognosis is guarded, recovery is often slow, and recurrence or relapse after treatment is common. Compared to bacteria, fungi grow more slowly and typically take longer to identify in the laboratory, so selection of definitive therapy is often delayed. In some cases, a specific organism may not be identified by culture but merely suspected as the cause of an enigmatic infection, so treatment remains empiric, based largely on the clinical acumen of the provider. The modern pharmacopeia of antifungal agents is broad, which has led to greater success in treating invasive fungal diseases while also highlighting nuances in drug selection, dosing, monitoring, and medication interactions that previously did not need to be considered.

**Call Out Box 9.1**

The term "fungi" refers to yeasts, molds, and other related organisms, including mushrooms. Taxonomically, fungi represent one of the biological kingdoms.

Yeast are microscopic unicellular fungal organisms that reproduce by budding.

Molds are fungal organisms that form multicellular filaments called hyphae. Heavy growth appears as a delicate fuzzy, often pigmented mass to the naked eye.

Dimorphic fungi exist in both yeast and mold forms based on the temperature at which they are growing.

**Call Out Box 9.2**

Dimorphic fungi that cause infections in humans include:

- *Histoplasma capsulatum*
- *Blastomyces dermatitidis*
- *Coccidioides immitis*
- *Paracoccidioides brasiliensis*
- *Sporothrix schenckii*
- *Cryptococcus neoformans*

## 9.2 Epidemiology

While rare fungal species may cause pneumonia in humans, there are several more common species that warrant empiric therapy when suspected of causing invasive disease. In addition, several antifungal medication options have broad activity against most yeast, molds, and dimorphic fungi, so for practical purposes, an understanding of the principles and pitfalls of fungal pneumonia in general is more important than an exhaustive review of every possible pathogen one might encounter in the specialty practice of clinical infectious diseases.

Fungal pneumonia is most concerning in patients with an underlying primary or secondary immune deficiency. While cellular immunity is certainly important for an effective host immune response to any fungal illness, defects in the numbers or function of neutrophils represent the greatest risk factor for acquiring fungal pneumonia. *Aspergillus* species are most commonly implicated as the cause of fungal pneumonia in patients with neutropenia or functional neutrophil defects such as chronic granulomatous disease. Pneumonia secondary to infection with *Candida* species is exceptionally rare and if present is usually only one manifestation of disseminated disease from hematologic seeding during periods of candidemia. Impairment in T-lymphocyte function is more typically associated with *Pneumocystis jirovecii* infection, the classic cause of opportunistic pneumonia in patients with advanced HIV infection, and with dimorphic fungal pneumonias [▶ Call Out Box 9.2].

The condition of allergic bronchopulmonary aspergillosis (ABPA) is an immunologic phenomenon primarily reported in patients with asthma, cystic fibrosis, and bronchiectasis from other causes. Treatment focuses on suppressing the hypersensitivity reaction with glucocorticoids, and although antifungal medication is typically used adjunctively to reduce airway mold colonization, the illness is not considered an infection. In the context of ABPA, the *Aspergillus* species is not invasive.

Transmission of fungal disease generally occurs through inhalation of environmental fungal spores. Human-to-human transmission does not occur. Deep fungal infections can also evolve if fungi encounter breaks in the skin or after incidental ingestion. These routes of transmission are unlikely to cause pulmonary disease unless a disseminating infection occurs. The risk of inhaling airborne spores is highest when individuals are in close proximity to construction sites or other areas where soil or vegetative matter is constantly disrupted. Windy, arid environments can also render soilborne spores airborne, making even casual outdoor activities a risk factor for some infections.

The most common causes of serious invasive or semi-invasive pulmonary fungal disease are *Aspergillus* species (◘ Fig. 9.1). *A. fumigatus* is seen most commonly, while *A. niger* and *A. terreus* also cause significant human disease. *A. terreus* is one of very few molds that are intrinsically resistant

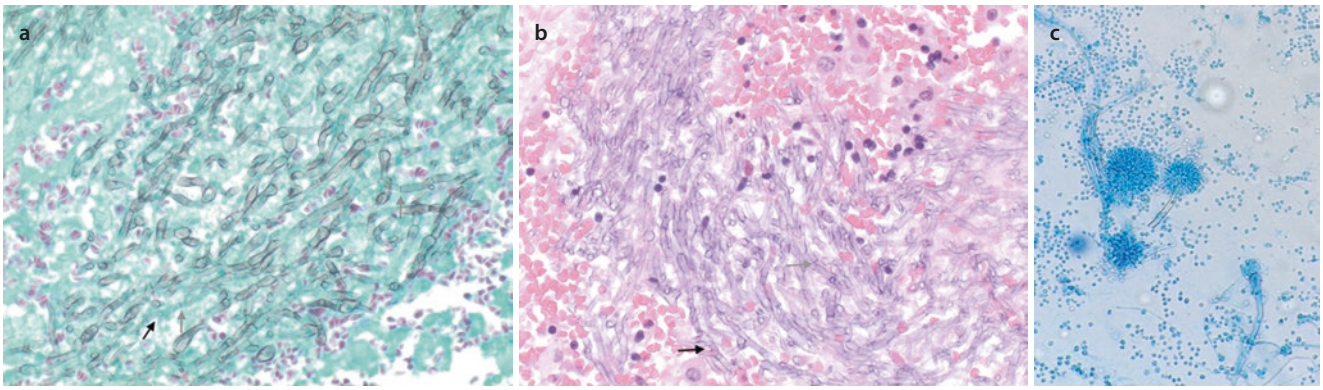


**Fig. 9.1** **a** Grocott methenamine silver (GMS) stain of an *Aspergillus* species collected from a patient with fungal pneumonia. 45° dichotomous branching (black arrow) is characteristic for this mold. The gray arrow shows a fungal septum. (Photograph courtesy of Dr. Mary D. Fiel-Gan M.D. Department of Pathology Hartford Hospital). **b** Hematoxylin and eosin stain of an *Aspergillus* species from a patient with fungal pneumonia. 45° dichotomous branching (black arrow) is characteristic for this mold. The gray arrow shows a fungal septum. (Photograph courtesy of Dr. Mary D. Fiel-Gan M.D. Department of Pathology Hartford Hospital). **c** Lactophenol cotton blue preparation of *Aspergillus fumigatus*. Phialides are present at the top of the conidiophore along with many loose, round conidia. (Photograph courtesy of Kimberly Hayes and Andrew Montero, Clinical Microbiology Laboratory, Hartford Hospital)

to amphotericin B. Other species of *Aspergillus*, such as *A. flavus* and *A. clavatus*, are infrequently reported to cause invasive human disease. Patients receiving treatment for hematologic malignancies are at high risk for developing pneumonia caused by *Aspergillus* species, particularly when their chemotherapy regimens are associated with prolonged periods of neutropenia and/or include high doses of systemic glucocorticoids. The degree of risk correlates directly with the patient's number of neutropenic days and then accelerates when the neutropenia persists beyond 3 weeks [1, 2]. Invasive and semi-invasive forms of pulmonary aspergillosis is uncommon in patients with advanced HIV infection presumably because their neutrophil function remains intact despite the presence of a serious T-cell immunodeficiency.

*Fusarium* species are other examples of molds that cause serious fungal pneumonia (Fig. 9.2). *Fusarium solani* is the most frequently observed species to cause human disease. Immunocompetent individuals may develop localized cutaneous infections, while immunocompromised hosts, especially those with hematologic malignancies or who have recently undergone a hematopoietic stem cell transplant, typically develop disseminated infection. *Fusarium* species are associated with high rates of fungemia with associated disseminated disease.

The *Mucorales* are an order of molds from the *Zygomycetes* class that include human pathogens in the *Rhizopus*, *Mucor*, and *Rhizomucor* genera. These molds have potential to cause opportunistic pneumonia but are most classically associated with erosive sinus infections [3]. The members of this mold family are intrinsically resistant to several antifungal agents, including voriconazole and micafungin, so infections should always be considered in high-risk individuals who receive these medications as prophylaxis for the prevention of candidiasis or aspergillosis. Infections have also been reported in patients with immune-compromising conditions such as poorly controlled diabetes and long-term steroid use [3, 4].

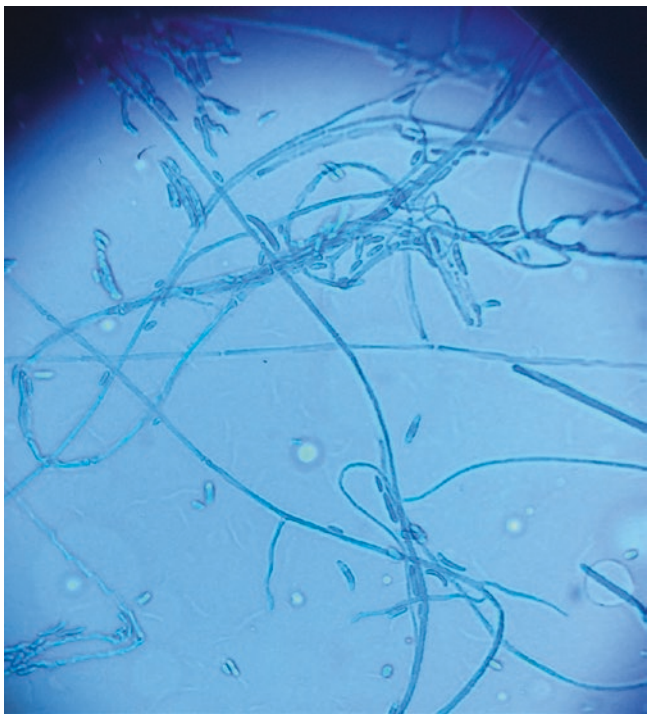

**Fig. 9.2** Lactophenol cotton blue preparation of a *Fusarium* species. Note the large curved macroconidia. (Photograph courtesy of Kimberly Hayes and Andrew Montero, Clinical Microbiology Laboratory, Hartford Hospital)

Geography plays a role in the acquisition of dimorphic fungal infections as several of the pathogens are endemic to specific regions. For example, *Coccidioides* species are present in the soil of the southwestern US states, Mexico, and parts of Central and South America (Fig. 9.3). *Coccidioides immitis* is found in the San Joaquin valley in California, whereas *Coccidioides posadasii* is more widespread. Infections are more common in the summer or fall.

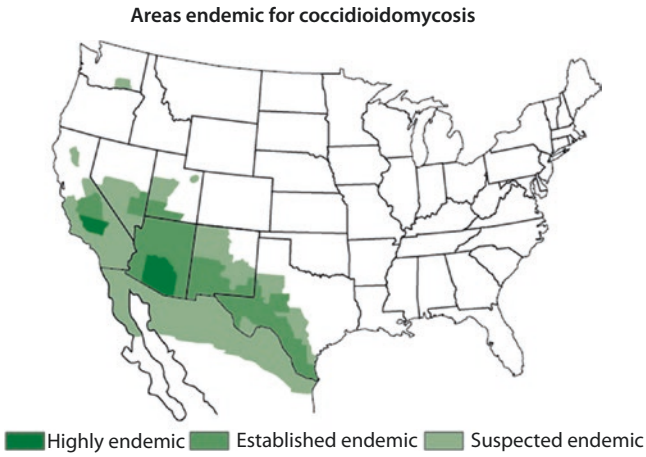


**Fig. 9.3** Areas of the USA that are endemic for coccidioidomycosis. (Image courtesy of CDC)

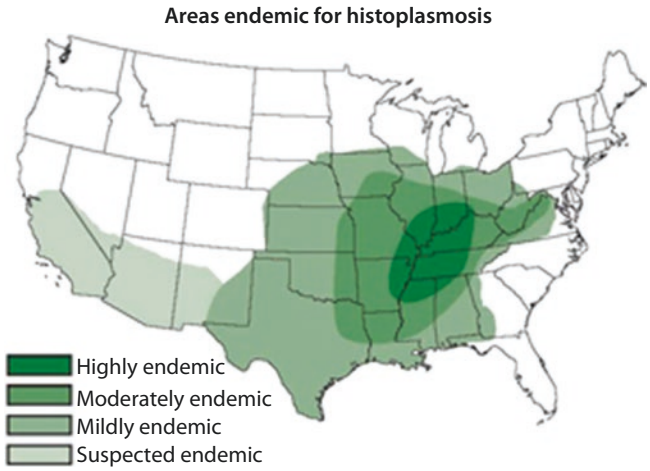


**Fig. 9.4** Areas of the USA that are endemic for histoplasmosis. (Image courtesy of CDC)

*Histoplasma capsulatum* and *Blastomyces dermatitidis* are more commonly found in the Central, Southern, and Mid-Atlantic States (Figs. 9.4 and 9.5), with *H. capsulatum* suspected to have a wider geographic area extending across much of the southern United States. Both fungi are found in plant detritus. Because *H. capsulatum* growth is enhanced by bat guano or bird droppings, it is also frequently found in places such as barns or caves [► Call Out Box 9.3].

Patients undergoing treatment with tumor necrosis factor antagonists and other similar biologic medications have also been shown to have higher risk of symptomatic and disseminated dimorphic fungal infection [5, 6].

## 9.3 Clinical Presentation

Fungal pneumonia can present insidiously. The diagnosis should be considered in patients who present with lower respiratory tract infection when appropriate risk factors are identified during the medical history. In some cases,


**Fig. 9.5** Areas of the USA that are endemic for blastomycosis. (Image courtesy of CDC)

**Call Out Box 9.3**
Social history, including occupation, hobbies, and travel, can often point to a specific fungal infection.

fungal pneumonia is an unexpected finding during the evaluation of a patient thought to have a normal immune system.

During the clinical evaluation, non-specific signs and symptoms such as fever and fatigue are typical. Patients develop a worsening dry cough, sometimes associated with pleuritic chest pain. Hemoptysis may occur. Clinicians should suspect fungal infection in patients who are sufficiently immunocompromised and/or are at risk of a specific dimorphic fungal infection when any of these symptoms are present, particularly for those who are not improving despite treatment with broad-spectrum antibiotics for presumed bacterial pneumonia.

*Aspergillus* species cause a spectrum of lower respiratory tract disease depending on the immunologic status of the host. Noninvasive aspergillosis occurs when preexisting lung damage has formed structural damage allowing the mold to colonize and then grow into a ball of hyphae called an aspergilloma. Semi-invasive disease occurs in moderately immunocompromised patients. Invasive infection is characteristic in those who are severely immunocompromised. The proclivity of *Aspergillus* species to be angioinvasive explains why hemoptysis is a common complication of pulmonary aspergillosis. Pulmonary infection with *Fusarium* species is clinically indistinguishable from invasive pulmonary aspergillus but is more commonly associated with documented fungemia.

Pneumonia secondary to one of the dimorphic fungi presents with dry cough, fever, and fatigue, typically occurring 1–3 weeks after exposure. In most immune competent patients, these infections are self-limited with symptoms resolving within several weeks of onset. More serious infections warrant treatment, as discussed below.

*H. capsulatum* causes a spectrum of pulmonary illness ranging from asymptomatic infection to fulminant pneumonia with disseminated disease. Acute histoplasmosis refers to illnesses of less than 1 month duration, and subacute disease is associated with symptoms lasting 1–3 months. Symptomatic infection lasting more than 3 months is deemed chronic. Chronic infection may result in the formation of lung granulomas, which tend to calcify over time. Calcified lung lesions are frequent incidental findings on chest radiographs performed years later for other reasons. Many such patients are unaware of their prior histoplasmosis infection. Significant mediastinal and other lymphadenopathy can occur with pulmonary histoplasmosis, resulting in compression symptoms on the airway or esophagus. Rarely, enlarged lymph nodes can compress the superior vena cava, leading to superior vena cava syndrome. A large inhaled inoculum of spores can result in diffuse pulmonary inflammation associated with significant dyspnea. The host inflammatory response to histoplasmosis can be associated with joint symptoms, pericarditis, and erythema nodosum.

Compared with histoplasmosis, blastomycosis tends to be a more chronic, invasive condition. Prolonged fever, night sweats, and weight loss are more common that reported for histoplasmosis. The cough of blastomycosis is more likely to be productive of sputum than cough associated with pneumonia secondary to other dimorphic fungi. As many as 10% of patients with blastomycosis have an acute, fulminant, and severe illness with respiratory distress syndrome. When the pneumonia presents in this manner, mortality approaches 50%.

## 9.4 Laboratory Diagnosis

The proper diagnosis of fungal respiratory infection requires careful consideration of the epidemiology and risk factors of the host, identifying and collecting the proper specimens, requesting the appropriate diagnostic tests, and proper processing of the specimen in the clinical microbiology laboratory [7–9].

**Selecting the proper patient specimen** The proper diagnostic clinical sample(s) depends on the fungi being considered. While less invasive techniques are preferable when collecting necessary samples, it is important to note that definitive identification of the etiologic agent often requires a tissue-based diagnosis. When the anatomic position of the lung lesions permit, bronchoscopy with transbronchial tissue sampling can be performed. Open lung biopsy may be necessary.

Antigen and antibody-based assays performed on serum can be helpful. *Aspergillus* species that is present in lung tissue sheds a cell wall component called galactomannan (GM) during replication. This component may be detectable in the patient's blood. GM antigen assays have varying sensitivity and specificity in different at-risk patient populations with both false-positive and false-negative results being reported, so care must be used in deciding when to test and how to interpret the result. For a patient with a high pretest probability of fungal disease, GM can be a useful tool to screen for and diagnosis pulmonary aspergillosis [10]. The GM assay only detects antigens shed from *Aspergillus* species. Another antigen-based assay, 1–3 beta-D-glucan (BG), detects cell wall components shed by *Aspergillus* species and many other fungi including *Pneumocystis jiroveci* and species of *Candida*, *Fusarium*, *Acremonium*, and *Trichosporon* [11]. Importantly, neither GM nor BG assays are able to detect the presence of the *Mucorales* family of fungi or *Cryptococcus neoformans*. Therefore, negative GM and BG serum results do not necessarily rule out fungal pneumonia. Additional specific serum antigen tests are also available for the detection of *Cryptococcus neoformans*, *H. capsulatum*, and *B. dermatitidis*. Acute and convalescent serum antibody tests can aid in the diagnosis of histoplasmosis, coccidioidomycosis, and blastomycosis [12–14].

**Call Out Box 9.4**
Positive respiratory cultures for candida should be treated with suspicion.

Sputum samples can be processed in the microbiology laboratory in an attempt to grow a suspected yeast or mold. During collection, the specimens can be contaminated with upper respiratory flora including *Candida* species, so results must be interpreted with caution when recovering fungi known to colonize the respiratory tract [▶ Call Out Box 9.4]. Sputum specimens are most sensitive for the recovery of *B. dermatitidis* when it is the cause of pneumonia. Other fungi can be recovered from sputum, but it is not usually the specimen of choice due to its poor sensitivity and specificity. Washings collected directly from the lower respiratory tract during bronchoalveolar lavage (BAL) are superior to sputum for recovery of fungal pathogens in culture. For some of the antigen-based assays, BAL fluid is superior to serum [15].

The preferred biologic sample for the diagnosis of fungal pneumonia caused by invasive fungi like *Aspergillus* species and members of the *Mucorales* family is tissue or fluid collected directly from the site of the infection. The tissue can be sent for fungal staining, culture, and in some instances molecular testing if necessary. Since collecting tissue or fluid involves an invasive procedure, the potential risks and benefits of collecting the ideal samples must be carefully assessed for each patient. If empiric therapy is administered based on radiographic findings and clinical suspicion alone, then close monitoring for any clinical response is critical. Failure to improve should trigger reevaluation for a tissue biopsy.

**Specimen ordering, handling, and transport to the clinical laboratories** For most clinical microbiology laboratories, fungal studies are not part of a routine culture so the desired tests must be requested separately. If there are any questions about what to order or if an unusual organism is suspected, it is recommended to call the microbiology and/or pathology

laboratories in advance for their guidance. Some fungi, such as *Aspergillus* species, will grow on the 5% sheep blood agar plates used to set up bacterial cultures, but specific orders for fungal studies will trigger the laboratory to inoculate culture media that is specifically designed to support and encourage the growth of mold. For any tissue samples, fungal staining and histopathology should also be requested. Examples of fungi that can be recovered from blood cultures collected specifically for fungal culture include *H. capsulatum*, *C. neoformans*, and *Fusarium* species.

After the specimen has been collected and placed into a sterile container, it should be transported directly to the laboratory at room temperature. If there is a delay of more than 2 h, then storage at 4 °C is preferred with transport to the microbiology laboratory within 24 h. Tissue specimens being sent to the anatomic pathology laboratory can be stored in formalin if it has been established that the specimen is not needed in the microbiology laboratory for culture purposes.



**Specimen processing in the microbiology and pathology laboratories** There are several fungal stains available to visualize fungal elements such as yeast or hyphae in primary clinical specimens. Examples include the periodic acid-Schiff, calcofluor-KOH, and the Grocott's methenamine silver (GMS) stains. Most tissue will also be initially stained with hematoxylin and eosin that may reveal fungal elements. When tissue-associated filamentous molds are identified microscopically, additional information about their morphology is also reported. The GMS stain is particularly useful for this purpose, allowing the pathologist or microbiologist to describe the number of hyphae present, whether the hyphae are broad or thin, the angle of hyphal branching, and the presence, paucity, or absence of septa. The traditional teaching is that *Aspergillus* species have thin, septated hyphae that grow in a pattern of dichotomous 45 degree branching. In contrast, *Mucorales* family fungi have broad, ribbon-like aseptate (or very few septa) hyphae that grow with 90 degree branching. Dimorphic fungi grow as yeast forms at human body temperature. When visualized microscopically in tissue sections of the lung, the pathologist will note the presence or absence of budding and describe their size and morphology. Based on these findings, an astute microbiologist or pathologist can usually name the offending pathogen.

Examples of classic yeast histopathology include the broad-based budding of *Blastomyces dermatitidis* compared with the narrow budding of *Cryptococcus* species. Small yeast that is present inside macrophages strongly suggests *Histoplasm*a species, whereas spherules with endospores are most suggestive of *C. immitis*. For an excellent review of the histopathologic diagnosis of fungi, please see Guarner, 2011 [8].

The definitive diagnosis of invasive fungal disease requires either the growth of the fungus in culture, preferably from tissue or the molecular detection of fungus-specific nucleic acid from biopsy tissue. Sabouraud agar is the most common culture medium used to isolate fungi in the microbiology laboratory. Growth can occur over several days to weeks depending on the organism. It is important to continue to monitor fungal cultures for growth beyond the typical 2–5 days used for bacterial cultures since some fungi are very slow growing. Most clinical laboratories will monitor fungal cultures for 6 weeks. When growth appears on Sabouraud media, the microbiologist will examine the color and morphology of the growing fungal colony. Once the colony has matured to form fruiting bodies, these are lifted from the colony with tape and visualized microscopically after staining with lactophenol cotton blue. The morphology of the fungal structures is used to determine the final identification of the mold. Definitive identification of yeast is now typically done using commercially available microbiology diagnostic platforms.

The morphological identification of molds in the clinical laboratory relies on the formation of fruiting bodies during culture, a process that can take several days to weeks. Newer techniques that reliably and rapidly identify fungi include polymerase chain reaction (PCR), DNA sequencing of ribosomal DNA, and matrix-assisted laser deionized-time of flight mass spectrometry (MALDI-TOF). Currently, these techniques are only applied to colonies of growing fungi and yeast with emerging literature suggesting that future applications may allow for their use on primary clinical specimens. MALDI-TOF is increasingly employed in clinical microbiology laboratories because it takes only minutes to identify an organism once growth has occurred. On occasion, a tissue sample may show fungal elements on staining with a negative culture result. In these situations, consultation with the clinical pathologist is warranted regarding the use of PCR directly on the tissue in an attempt to amplify fungal-specific DNA for definitive identification. This is typically done by reference laboratories and can provide valuable information to the clinician when an organism is unlikely to be recovered in the microbiology laboratory for identification.

## 9.5 Treatment of Fungal Pneumonia

Table 9.1 summarizes the antifungal properties of polyenes, triazoles, and echinocandins, the three most common classes of medication used to treat invasive fungal pneumonia. Recommended first-line, alternative, and salvage therapies are provided for each pathogen.

*Aspergillus* species are the most common fungi to cause pneumonia. The drug of choice to treat invasive pulmonary aspergillosis is voriconazole. Treatment should be administered intravenously to begin and then switched to oral therapy when the patient demonstrates clinical improvement [16, 17]. Therapeutic drug monitoring is necessary when using voriconazole to ensure adequate blood concentrations and minimize toxicities. This is particularly important in monitoring the treatment of patients that are critically ill, at the extremes of ages, obese, suspected of breakthrough/resistant infection, and/or have signs or symptoms concerning for drug toxicity [17].

**Table 9.1** Summary of commonly used antifungal agents[a]

| Class | Mechanism | Agents and dosing | Monitoring |
|---|---|---|---|
| Polyene | Binds to ergosterol in fungal cell membrane causing instability and cell death | Traditional amphotericin B:<br>Blastomycosis and histomycosis: 0.7–1 mg/kg/day<br>Coccidioidomycosis: 0.5–1 mg/kg/day<br>Mucormycosis: 1–1.5 mg/kg/day<br>Liposomal amphotericin B[b]:<br>Aspergillus, blastomycosis, histoplasmosis: 3–5 mg/kg/day<br>Coccidioides: 5 mg/kg/day<br>Mucormycosis: >5 mg/kg/day<br>Lipid complex amphotericin B:<br>Mucormycosis: 5 mg/kg/day | Serum potassium, magnesium, serum creatinine, LFTs, bilirubin |
| Triazoles | Inhibit cytochrome P-450 enzymes that are needed to produce ergosterol. Results in cell membranes without ergosterol leading to instability and cell death | Fluconazole:<br>Coccidioidomycosis<br>Adult 400–1200 mg/day<br>Pediatric 6–12 mg/kg/day<br>Histoplasmosis<br>Adult: 800 mg/day<br>Pediatric: 3–6 mg/kg/day (maximum 200 mg/day)<br>Isavuconazole<br>Adult: Intravenous or oral 200 mg (base) Q8h × 2 days – load, then 200 mg daily beginning 12–24 h after last of loading dose<br>Itraconazole oral:<br>Aspergillosis:<br>Adults: 200 mg BID or initial therapy with 200 mg TID for 3 days then 200 mg BID<br>Pediatric – No specific dosing recommendation provided<br>Blastomycosis<br>Adult: 200 mg TID for 3 days then 200 mg BID<br>Pediatric: 10 mg/kg/day divided BID (maximum 400 mg/day)<br>Coccidioidomycosis:<br>Adult 200 mg BID – TID<br>Pediatric: 2–5 mg/kg/dose TID for 3 days then BID OR 5 mg/kg/dose BID (maximum 200 mg/dose)<br>Histoplasmosis<br>Adult: 200 mg TID for 3 days then 200 mg BID.<br>Pediatric 5–10 mg/kg/day divided BID or 2–5 mg/kg/dose TID for 3 days followed by BID (max 200 mg/dose)<br>Posaconazole<br>Aspergillus<br>Adult: Intravenous or delayed release tablet 300 mg BID × 1 day then 300 mg daily; suspension 200 mg TID<br>Pediatric: No specific recommendation on dosing provided<br>Histoplasmosis, coccidioidomycosis<br>Adult: 400 mg Q12h[c]<br>Mucormycosis<br>Adult: 200 mg four times a day or 400 mg BID[c]<br>Pediatric (>/=2 years and < 34 kg): 18–24 mg/kg/day in four divided doses (maximum 800 mg/day)<br>Voriconazole:<br>Aspergillus, coccidioidomycosis, histoplasmosis<br>Adults (>50 kg): Intravenous 6 mg/kg Q12h × 1 day then 4 mg/kg Q12h; oral 200–300 mg Q12h or weight-based dosing as listed for intravenous<br>Pediatric (<50 kg): Intravenous or oral 9 mg/kg BID (maximum 350 mg/dose)[d] | Signs/symptoms of GI intolerance and neurologic symptoms, LFTs, electrolytes (e.g., potassium), EKG for arrhythmias such as torsade de pointes and bradycardia, triglycerides, therapeutic drug trough itraconazole of 0.5–1 mg/l & < 3 mg/L (or > 1.5 mg/l combination itraconazole and metabolite); or random level of 1 to 10 mcg/ml combination; voriconazole (>1–1.5–<5–6 mg/l) and posaconazole (>1.25 mg/l or > 1.8 mg/l); Voriconazole should also be monitored for photopsia, periostitis, and skin reactions (e.g., rashes, Stevens-Johnson syndrome, prolonged use skin cancer and melanoma) Isavuconazole, like voriconazole, should also be monitored for photosensitivity and visual disturbances |

(continued)

**Table 9.1** (continued)

| Class | Mechanism | Agents and dosing | Monitoring |
|---|---|---|---|
| Echinocandin | Inhibit 1,3 beta-glucan synthase, an important component of fungal cell walls, leading to cell death | Caspofungin:<br>Adults: 70 mg/day × 1 day then 50 mg daily<br>Pediatric: 70 mg/m$^2$/day × 1 dose then 50 mg/m$^2$/day<br>Micafungin:<br>Adult: 100–150 mg/day<br>Pediatric (<40 kg): 2–3 mg/kg/day (higher doses for younger, especially infants where doses as high as 8.6 mg/kg have been reported)<br>Anidulafungin: Limited data as monotherapy for aspergillus therapy. Guidelines do not recommend | LFTs and serum potassium |

*LFTs* liver function tests including AST, ALT, and bilirubin, *BID* twice daily, *TID* three times a day
[a]Dosing is for patients with normal renal and hepatic function without drug interactions that would affect antifungal concentration
[b]Higher doses have not shown improved outcome but did show increased toxicity in aspergillus infections. Small study of mucormycosis suggests that the higher dosage may have a potential benefit
[c]Much of the initial evidence existed prior to the availability of the extended release tablet. The use of the extended release tablet is expected to provide higher serum concentrations of posaconazole. Doses should be modified based upon level determination
[d]Pediatric dosing only studied for aspergillosis



If voriconazole cannot be used, liposomal amphotericin B is the best alternative. Some patients are unable to take voriconazole due to medication interactions or allergy, while others may be suspected or proven to have an infection caused by a voriconazole-resistant isolate. Cross-resistance between voriconazole and polyenes has not been demonstrated [17, 18]. Alternative therapies include other lipid-based amphotericin B products, itraconazole, and isavuconazole [17]. Salvage therapy options include echinocandins, posaconazole, and combination therapy [17]. Treatment is typically prolonged as it should be continued until clinical and radiographic resolution is demonstrated [16].

Infections caused by *Fusarium* species are particularly difficult to treat as the mold exhibits increased resistance to all available antifungal therapies. High doses of amphotericin B are usually required. Patients tolerate the lipid and liposomal formulations of amphotericin B much better than the deoxycholate salt, but at these doses, some degree of renal toxicity is virtually guaranteed. If the high doses of amphotericin B can be tolerated, the medication can be effective [19]. If amphotericin B cannot be used, triazole therapies that might offer some benefit include voriconazole, posaconazole, and isavuconazole. Echinocandins have no activity against *Fusarium* species.

Pneumonia and other invasive infections caused by members of the *Mucorales* family of fungi should be treated both medically and surgically. High-dose liposomal or lipid complex amphotericin B is the drug of choice. Early and aggressive surgical debridement is also necessary to achieve a cure [20, 21]. Patients with suspected *Mucorales* infections who are neutropenic should receive granulocyte colony-stimulating factor in addition to their antifungal therapy [20] since recovery of their neutrophil counts is required to achieve a cure. Salvage therapies include posaconazole, lipid amphotericin in combination with either posaconazole or caspofungin [20]. When immediate release posaconazole is used, it should be administered four times daily to optimize absorption [20]. *Mucorales* are intrinsically resistant to voriconazole. Invasive infections caused by members of molds included in this family are well-described among those high-risk patients who have been treated with voriconazole prophylactically in an effort to prevent pulmonary aspergillosis [▶ Call Out Box 9.5].

**Call Out Box 9.5**
*Fusarium* and the *Mucorales* have intrinsic drug resistance to many antifungal medications including all of the echinocandins and some of the triazoles.

## 9.6 Treatment of Pneumonia Caused by Dimorphic Fungi

The optimal treatment for invasive infection caused by dimorphic fungi is pathogen specific. Pulmonary histoplasmosis does not always merit treatment since mild, self-limiting illness is typical in otherwise healthy individuals. When therapy is indicated for mild to moderate disease, oral itraconazole should be used [16, 22]. Amphotericin B lipid complex or liposomal formulation is the first-line antifungal therapy for severe disease or for azole therapy failures. Amphotericin B deoxycholate is an alternative and despite its high rate of moderate-to-severe side effects is still considered by some as first-line therapy for pediatric patients [22, 23]. Methylprednisolone (0.5–1 mg/kg/day intravenously) should be added as adjunctive therapy in patients with histoplasmosis who are experiencing hypoxemia or respiratory distress [16, 22]. Itraconazole is recommended as oral therapy after 2 weeks of intravenous

therapy with amphotericin B if there has been interval clinical improvement [22]. The total duration of therapy is for at least 12 weeks, and immunosuppressed patients may require treatment for a year or longer. Decisions regarding total length of treatment depend on the patient's clinical response, their immune status, and observed trends in urine and serum histoplasma antigen concentrations [5, 16, 22, 23]. Blood itraconazole concentrations should be obtained after 2 weeks of therapy to ensure absorption since its bioavailability is low. Liquid itraconazole suspension should be used since it has superior bioavailability over itraconazole pills [22]. Based upon limited data, fluconazole, voriconazole, or posaconazole are salvage options [16, 24]. Isavuconazole has very limited, mixed data for the treatment of pulmonary histoplasmosis. As such, it should only be used when other agents are contraindicated or unavailable [25]. Echinocandins should never be used to treat histoplasmosis [22].

Recommended treatments for pulmonary blastomycosis are similar to those used for pulmonary histoplasmosis. Mild to moderate infections are treated with oral itraconazole monotherapy, while severe disease is treated initially with amphotericin B. The patient can be transitioned to oral itraconazole after a week or two of intravenous amphotericin B assuming they have shown a good clinical response [16, 26]. Treatment with voriconazole or posaconazole is reserved for salvage therapy as data on effectiveness are very limited [25–27]. Echinocandins should never be used to treat blastomycosis.

Coccidioidal infection is similar to histoplasmosis and blastomycosis as immunocompetent patients with asymptomatic lung infection are generally not treated. Initial antifungal therapy is indicated for patients with symptomatic coccidioidal pneumonia, asymptomatic patients with HIV infection who have a CD4+ T-lymphocyte count of less than 250 cells/mm$^3$, diabetic patients, and individuals considered to be frail. An oral triazole such as fluconazole is the drug of choice for initial therapy. Itraconazole is an alternative [28]. In cases where the patient has failed multiple surgeries, has ruptured coccidioidal cavities, or for whom triazole therapy is not an option (e.g., pregnancy or toxicity concerns), amphotericin B therapy should be considered [28]. Voriconazole, posaconazole, or isavuconazole can be used for salvage therapy as each has shown potential success in a limited number of patients [25, 28]. The antifungal therapy duration is usually at least 3 months for uncomplicated acute coccidioidal pneumonia. Decisions on length of therapy needed are determined based on clinical, laboratory, and radiological responses to treatment over time. At least 1 year of therapy is indicated for chronic coccidioidal pneumonia [28].

## 9.7 Considerations When Choosing Between Available Antifungal Medications

Potential drug interactions and adverse effects must be considered carefully when choosing initial antifungal therapy as these issues may limit therapeutic options. Patients who develop fungal pneumonia are often immune suppressed and undergoing treatment with a variety of drugs, including cancer chemotherapy or transplant rejection medications. Nephrotoxicity is a common limiting side effect of amphotericin B therapy, for example, and this risk is increased when amphotericin B is administered along with other nephrotoxic medications.

Amphotericin B, currently available triazoles, and pentamidine can all prolong the QTc interval on the electrocardiogram [17, 29]. The risk of QTc prolongation is increased when multiple QTc-prolonging medications are given at the same time and/or when patients are of advanced age, have underlying electrolyte abnormalities, or have baseline long QT syndrome. Prolongation of the QTc interval places the patient at risk for developing torsades de pointes, a life-threatening form of ventricular tachycardia that can degenerate into ventricular fibrillation. Therefore, amphotericin B, triazoles, and pentamidine should be used with caution in these settings [17, 29]. An excellent, free resource to that lists the QTc-prolonging potential of medications can be found at ▶ www.crediblemeds.org [29].

Antifungal medications also have potentially significant interactions with cytochrome P450 (CYP) metabolism. Triazoles have demonstrated significant in vivo inhibition of the 3A4/5 (all triazoles) and 2C9 (fluconazole, itraconazole, and voriconazole only) isoenzymes [17, 30]. National guidelines for the treatment of aspergillosis and opportunistic infections provide specific recommendations regarding triazole interaction with other drugs, including the frequency of drug level monitoring, which medications are contraindicated under given circumstances, and when medication dosing should be altered to preserve the expected effect and limit or reduce the possibility for adverse effects [17]. For example, mold-active azoles such as voriconazole should be avoided when vincristine is needed for chemotherapy because the azole dramatically extends the serum half-life of the vincristine. Persistently elevated vincristine levels have a strong association with symptomatic neuropathy. Doses of calcineurin inhibitors (cyclosporine, tacrolimus) or mTOR kinase inhibitors (sirolimus) should be decreased when triazoles are being co-administered. Methotrexate should not be co-administered with isavuconazole [17].

In contrast, echinocandins (caspofungin, micafungin, anidulafungin) have relatively few established drug-drug interactions. These antifungal drugs do alter calcineurin inhibitor and mTOR kinase inhibitor levels so concentrations should be monitored when echinocandins are co-administered [31].

Patients who are being treated with rifampin should be carefully assessed when additional medications become necessary because drug interactions are so frequent. Rifampin is a potent inducer of many hepatic cytochrome P450 (CYP) enzymes and as such should be avoided when possible in patients receiving atovaquone, dapsone, or any of the available triazoles. Caspofungin can be used safely, but a higher dose is necessary to account for the more rapid clearance in the presence of rifampin-associated CYP induction [17, 31].

There are many other CYP interactions that exist, especially in patients with HIV infection or those receiving immunosuppressant medications for transplant. These interactions should be evaluated using the respective guidelines or Flockhart's clinically relevant P450 drug interactions table available at: ► http://medicine.iupui.edu/CLINPHARM/ddis/clinical-table [32].

## Case Study

### Practical Examples

**Case 1**

A 17-year-old male receiving treatment for acute myelogenous leukemia develops fever and dry cough during a period of chemotherapy-induced neutropenia. His absolute neutrophil count is zero, and his last round of chemotherapy was 2 weeks ago. He is hospitalized and treated empirically with broad-spectrum antibiotics. Fevers and cough persist despite 3 days of antibiotic treatment. Blood cultures remain negative. Fluconazole therapy is initiated, but the cough worsens and he develops hypoxemia. During discussions with the family, it is revealed that the patient had been helping his father with an ambitious kitchen remodeling home improvement project prior to his hospitalization.

This patient is at particularly high risk for developing pulmonary aspergillosis and certainly warrants further evaluation for the source of his persistent fever. A computerized tomogram scan of his chest may reveal abnormalities that are not apparent on a chest radiograph. Serum antigen testing for galactomannan and beta-D-glucan should be arranged prior to initiating empiric therapy that includes coverage for aspergillosis. Fluconazole is not effective against this genus of mold. Voriconazole is the drug of choice unless contraindicated due to drug interactions such as prolonged QT. If voriconazole cannot be used, empiric treatment with amphotericin B or with an echinocandin such as caspofungin or micafungin is appropriate. Consultation with a pulmonologist or surgeon may be necessary to facilitate the collection of samples from the lower respiratory tract for fungal culture and histopathology.

**Case 2**

A previously healthy 34-year-old woman presents with low-grade fevers, generalized muscles aches, and a worsening dry cough that began 1 week earlier. One month ago, she reports that she went on a horse-riding expedition through the San Joaquin valley. Her physical examination is unremarkable. She has no significant past medical history.

Low-grade fever, muscle aches, and dry cough are common symptoms of an acute respiratory tract infection. The potential list of causative agents is quite long and should include pulmonary coccidioidomycosis based on her recreational activity in an endemic area. Since she has no chronic medical conditions, coccidioidomycosis would very likely be a self-limited infection. Therefore, empiric therapy would not be indicated at this time, although it would be reasonable to perform serologic testing to confirm that somewhat unusual diagnosis. A chest radiograph may be normal or show patchy or nodular infiltrates. Should this young woman develop progressive symptoms or worsening chest pain, oral fluconazole or intraconazole are reasonable first-line treatment options as they may hasten her recovery.

**Case 3**

A 50-year-old man with history of rheumatoid arthritis, treated with infliximab and oral methotrexate, is seen in the emergency room for symptoms of coughing, wheezing, and chest pain that worsens with cough and when he takes a deep breath. His chest radiograph reveals mediastinal adenopathy and multiple scattered nodular opacities in both lungs. He is an avid outdoorsman. During a recent weekend camping trip, he slept on the ground in a bivouac. His symptoms began less than a week later and have worsened with time.

The patient's history and underlying risk factors are suggestive of acute pulmonary histoplasmosis. Given his ongoing treatment with infliximab and its associated immune suppression, he is at substantial risk for developing disseminated disease. It is important to confirm the diagnosis, preferably through collecting lower respiratory samples for culture via either bronchoalveolar lavage or mediastinal biopsy. Serum and urine histoplasma antigen testing should be performed, and serologies requested.

While itraconazole is a reasonable oral option to treat uncomplicated histoplasmosis, intravenous amphotericin B (lipid complex or liposomal) is the preferred initial therapy in this patient because of his clinical status and his risk for further deterioration. Transition to oral itraconazole is appropriate after 2 weeks of amphotericin B therapy if his symptoms are improving.

**Case 4**

A 25-year-old woman recently underwent hematopoietic stem cell transplant to treat a relapsed leukemia. She has not yet fully engrafted. One week ago, she developed fevers and nasal congestion. Empiric treatment with antibiotics has not provided relief from the fevers, and she has now developed a worsening cough with dyspnea. Micafungin therapy was administered empirically, but her respiratory illness continued to worsen. A computer tomography scan of her chest showed multiple areas of dense circular pulmonary infiltrates with "halo signs" around them. Blood cultures obtained while on antifungal therapy are reported positive for mold after several days of incubation. Testing for beta-D-glucan is positive, and galactomannan antigen testing is negative.

It is very likely that this woman has *Fusarium* species pneumonia with disseminated infection. Treatment should be switched immediately to intravenous liposomal amphotericin B (high-dose). Some species of *Fusarium* are susceptible to voriconazole or posaconazole, but *F. solani*, the most common species, is not. All *Fusarium* species are intrinsically resistant to echinocandin class antifungal medication, including micafungin.

## 9.8 Exercises

Please refer to the supplementary information section for answers to these exercises.

1. Think about how you might manage a patient with new pulmonary nodules found on chest imaging that is performed as part of a diagnostic evaluation for possible pneumonia. Given the appropriate concern for the presence of a dimorphic fungal infection:
   A. What aspects of the clinical history help you make a provisional clinical diagnosis?
   B. What laboratory tests would you perform?
   C. Why is it important to identify a specific organism?

2. Discuss the risk factors associated with developing fungal pneumonia in patients undergoing treatment for a hematologic malignancy.
   A. How does the cancer diagnosis complicate the treatment of the infection?
   B. Conversely, how does development of a fungal pneumonia complicate the treatment of the malignancy?

3. Discuss the advantages and disadvantages of the echinocandin class of antifungals, in terms of empiric and definitive therapy.
   A. How might the spectrum of activity of echinocandins limit their use under certain circumstances?
   B. How do drug-drug interactions, and adverse effects of the echinocandins compare relative to alternative agents that might be used to treat the same organisms?

## 9.9 Summary

Fungal pneumonia is an uncommon but serious condition more typically seen in patients who are significantly immunocompromised. *Aspergillus* species are the most likely pathogen to affect high-risk individuals, but a full history of possible exposures should always be obtained to help guide the complete evaluation. Factors such as prior treatment with antifungal medications; environmental, recreational, and occupational exposure; and geographic location need to be considered when assessing the risk for infection with the *Mucorales*, dimorphic fungi, or resistant variants of more common yeasts and molds. The diagnosis of fungal pneumonia often depends upon obtaining specimens via bronchoscopy or open lung biopsy, although serologic and antigen testing also play a role in making presumptive diagnoses. Although newer antifungal agents such as voriconazole, posaconazole, and isavuconazole and the echinocandin class of medications exhibit broad-spectrum activity against several yeasts and molds, there remains a primary role for amphotericin B in the treatment of specific fungi such as members of the *Mucorales*. Drug toxicities and drug-drug interactions are frequent complications of treatment regimens that include antifungal drugs. When available, therapeutic drug monitoring is recommended to optimize clinical outcomes.

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# Infections of the Heart

Contents

# Infective Endocarditis

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**Learning Objectives**

- Recognize clinical manifestations associated with infective endocarditis
- Describe the risk factors associated with infective endocarditis
- Understand criteria for the diagnosis of infective endocarditis
- Discuss treatment options for infective endocarditis
- Identify strategies used to prevent infective endocarditis

## 10.1 Introduction to the Problem

Infective endocarditis (IE) is a rare but well-described occurrence. IE occurs when pathogens adhere to the endocardium, the inner lining of the cardiac chambers, or the cardiac valves. Disruption of the cardiac endothelium predisposes patients to the development of IE. Platelets and fibrin deposit on damaged endothelium forming a thrombus. Pathogens adhere to this thrombus and form an infected vegetation. Embolization from this infected thrombus can result in metastatic infection.

The pathogenesis of IE is dependent on two important factors: (1) damaged or denuded cardiac endothelium and (2) virulence factors of the infecting pathogen [1]. Cardiac endothelium can become damaged by turbulence from jets of blood caused by anatomic abnormalities such as stenotic valves or septal defects. Direct damage of the cardiac endothelium can also result from contact with an indwelling venous catheter. Colonization of the thrombus that forms at the site of damaged endothelium can occur during periods of bacteremia or fungemia. This colonization can happen during periods of transient bacteremia, such as those that follow toothbrushing, dental and other medical procedures, or straining to stool [1, 2]. Additionally, direct infection of indwelling devices such as pacemaker leads or mechanical valves can occur at the time of surgical placement.

Gram-positive organisms are the most common cause of IE. Laboratory studies demonstrate that many gram-positive organisms possess cell surface structures, called adhesins, which attach to host cells and enhance the organism's ability to cause IE [1]. These structures may also play a role in evasion of the host immune response. Staphylococci can form a biofilm, especially on devices and prosthetic material. Adhesins appear important in biofilm development and maturation [3]. Biofilm is difficult to penetrate both for antimicrobials and for host immune cells, and its presence may allow for prolonged pathogen survival.

In developed countries, most cases of pediatric IE occur in children with congenital heart disease (CHD) or children with a history of prior cardiac surgery. Improved survival following cardiac surgery in children with complex CHD may contribute to increasing incidence of pediatric IE among these patients. In developing countries, with higher incidence of acute rheumatic fever, rheumatic heart disease remains an important risk factor for development of IE in children and in adults. The incidence of IE among children varies between published studies, but a recent multicenter study reported an incidence of 0.05–0.12 cases per 1000 pediatric hospital admissions [4] [▶ Call Out Box 10.1].

**Call Out Box 10.1**

- Most cases of pediatric IE occur in children with CHD or prior cardiac surgery
- Rheumatic heart disease remains an important risk factor in developing countries

## 10.2 Definitions

***Acute bacterial endocarditis*** - Infection of the cardiac endothelium associated with a fulminant disease course

***Subacute bacterial endocarditis (SBE)*** - Infection of the cardiac endothelium associated with an indolent disease course, which may be 6 weeks or longer

***Osler nodes*** - Tender, subcutaneous nodules on the pads of the fingers and toes

***Janeway lesions*** - Non-tender macular lesions on the palms and soles

***Roth spots*** - Hemorrhagic retinal lesions with pale centers

## 10.3 Basic Concepts

### 10.3.1 Clinical Manifestations

Initial symptoms of IE are non-specific. Fever, malaise, and anorexia are common. Non-specific symptoms may persist for weeks in cases of subacute IE. However, in cases of acute endocarditis, symptoms can rapidly progress to a sepsis-like illness. Young children and adolescents with IE can have mixed features of acute and subacute disease [5]. The lack of specificity of symptoms associated with IE can delay the diagnosis. Significant morbidity and mortality can result from unrecognized IE because of the delay in effective treatment. The severity of cardiac dysfunction and the degree of metastatic disease impact clinical manifestations [6].

Cardiac murmurs are common in patients with IE. Significant change in an existing murmur may indicate the presence of IE, but often these changes are subtle. Splenomegaly is associated with IE. A careful physical examination may reveal Osler nodes, Janeway lesions, and/or Roth spots, findings that are more common in adults than in children. Infectious emboli to the lungs are commonly seen with involvement of the right-sided heart valves, while emboli to the central nervous system, spleen, and extremities are typical of left-sided valve infection. Central nervous system emboli are especially worrisome because of the potential for cerebral ischemia or hemorrhage and its morbidity [▶ Call Out Box 10.2].

**Call Out Box 10.2**
**Clinical Manifestations of IE**

- Fever, malaise, and anorexia are common initial symptoms of IE.
- The non-specific nature of symptoms can delay diagnosis of IE.
- Acute presentation with rapid progression of life-threatening illness can occur.
- Cardiac murmurs are common in patients with IE.
- Extracardiac manifestations of IE are more commonly seen in adults than in children.

### 10.3.2 Risk Factors

Structural cardiac disease predisposes patients to the development of IE. However, some defects may be silent, such as the presence of a bicuspid aortic valve, and not identified until the episode of endocarditis. Surgical correction of septal defects and patent ductus arteriosus eliminates the attributable risk for IE if no residual defect persists, but surgery itself may be an independent risk factor for developing IE [1]. During the immediate postoperative period, the risk of IE is low for most cardiac defects. However, in patients with residual hemodynamic issues after prosthetic valve or conduit placement, a higher risk for IE exists in the immediate postoperative period. Patients who have corrective surgery for complex congenital heart disease have a long-term, perhaps life-long, risk for IE. Residual cardiac defects and the presence of prosthetic material increase this risk. Residual defects after transcatheter device placement may also be a risk factor for IE [1].

Neonates are susceptible to IE and the incidence in this population has increased [1]. The presence of indwelling central venous catheters increases the risk for development of IE in all patients, including neonates. Intravenous drug use also increases the risk for development of IE and should be considered as a potential predisposing factor in adolescents and adults who appear to have no other predisposing risks. IE secondary to intravenous drug use is most commonly on the right side of the heart, especially involving the tricuspid valve. IE can occur in patients without underlying cardiac disease or other identifiable risk factors [► Call Out Box 10.3].

**Call Out Box 10.3**
**Risk Factors for Developing IE**

- Structural heart disease and prior cardiac surgery are risk factors for IE.
- Indwelling central venous catheters increase risk for development of IE.
- IE can occur in children without identifiable risk factors.

### 10.3.3 Pathogens that Cause Infective Endocarditis

Staphylococci, viridans group streptococci, and *Enterococcus* species are the most common pathogens implicated in cases of IE. *Staphylococcus aureus* bacteremia can result in IE in patients with and without underlying valvular or other cardiac disease. *S. aureus* is the most common cause of IE in individuals without underlying structural cardiac disease or other known risk factors, and the most common cause of acute (fulminant) endocarditis [1, 7]. Sustained bacteremia is common in patients with *S. aureus* IE even after appropriate antimicrobial therapy has been initiated. Fevers may also persist for a week or longer. Coagulase-negative staphylococci cause a much smaller proportion of IE than does *S. aureus*. IE caused by coagulase-negative staphylococci is more indolent in presentation but remains an important cause in neonates, individuals with prosthetic valve endocarditis, and among patients with long-term indwelling central venous catheters. *Staphylococcus lugdunensis* is a coagulase-negative staphylococcus that often mimics the more virulent disease caused by *Staphylococcus aureus*, whether it's causing IE or another deep tissue infection.

In most studies, viridans group streptococci are the most frequently identified cause of IE [1, 7]. These organisms colonize the human mouth and gastrointestinal tract. Transient bacteremia is not uncommon from minor mucosal trauma, dental procedures, toothbrushing, or poor dental hygiene, but most are cleared quickly by the patient's innate immune response. Such bacteremias can be sufficient to seed and infect an abnormal heart valve, leading to the development of viridans group streptococcal IE. Enterococci have a similar potential, causing IE to occur more commonly in adults than in children.

Gram-negative organisms are an uncommon cause of endocarditis. HACEK group organisms (*Haemophilus* species, *Aggregatibacter (previously Actinobacillus)* species, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella* species) are fastidious gram-negative organisms that colonize the oropharynx of humans and cause a minority of pediatric IE. By definition, fastidious gram-negative organisms will not grow on MacConkey agar, a microbiological culture medium designed to be selective and differential for most gram-negative bacteria. Of the HACEK organisms, *Kingella kingae* and *Aggregatibacter* (formerly *Haemophilus*) *parainfluenzae* appear to be the most common causes of pediatric IE [8]. Enteric gram-negative rods (*Enterobacteriaceae*, such as *Escherichia coli* and *Klebsiella* species) are a relatively common cause of catheter-related blood stream infection, especially among patients with underlying gastrointestinal tract disease but are a rare cause of IE [1].

Though common in the pre-antibiotic era, beta-hemolytic streptococci (e.g., *S. pyogenes*, *S. agalactiae*) and *S. pneumoniae* IE cases are much less frequently encountered today. Reports of IE caused by other bacteria do occur, but these represent a small proportion of all cases. Fungal endocarditis is rare beyond the neonatal age, where its niche

lies among premature infants with long-term indwelling venous catheters. *Candida* species are the most common cause of fungal IE.

In approximately 5% of cases of IE (higher in some centers), blood cultures are negative despite clinical or echocardiographic evidence of IE. This situation is typically termed culture-negative endocarditis and may be secondary to recent antibiotic therapy that has suppressed the growth of the offending organism in the laboratory, or from an infection caused by a fastidious or difficult to isolate pathogen, including *Bartonella* species, *Coxiella burnetii*, *Chlamydia* species, *Brucella* species, *Legionella* species, *Tropheryma whipplei*, and non-*Candida* fungi.

### 10.3.4 Approach to the Diagnosis of IE

Due to the typically indolent presentation of IE, the differential diagnoses may, at first evaluation, be quite broad. In cases of acute presentation, sepsis or causes of inflammatory cardiac dysfunction such as myocarditis or pericarditis should be considered. In cases of subacute bacterial endocarditis, indolent infections such as endemic mycoses (*Histoplasma capsulatum*, *Blastomyces dermatitidis*, or *Coccidioides immitis*) or nontuberculous mycobacterial infections may be considered depending on the patient's risk factors for these infections and specific presenting symptoms. Noninfectious causes of fever such as inflammatory and autoimmune conditions should also be considered.

The American Heart Association (AHA) published an updated scientific statement about IE providing recommendations regarding its diagnosis and management [1]. These recommendations are based on available evidence and expert consensus. Readers are encouraged to consult AHA statements for detailed recommendations on the diagnosis and management of IE and to review updates to these recommendations from the AHA as these become available. Due to the variability in clinical presentation of IE, criteria for stratifying the likelihood of a diagnosis of IE were developed by Durack et al. in 1994 [9]. These criteria, known as the Duke criteria, have been modified since their original publication [10]. The modified Duke criteria (► Box 10.1 and 10.2) are considered helpful to establish a diagnosis of IE. The diagnosis is based on clinical features, microbiological evidence, and echocardiogram findings.

Blood cultures should be collected for patients in whom IE is suspected, especially from those with fever of unexplained origin and one of the following: pathological cardiac murmur, history of cardiac disease, or history of endocarditis. It is recommended to collect multiple blood culture samples in patients suspected of having IE. Due to the fastidious nature of some organisms implicated in IE, discussion with the microbiology laboratory about methods to increase the yield of blood culture should be considered, including the use of molecular diagnostic testing and serologic studies for culture-negative cases. Other non-specific laboratory abnormalities associated with IE include elevated erythrocyte sedimentation rate, elevated C-reactive protein, hematuria, anemia, presence of rheumatoid factor, and low serum complement.

**Box 10.1 Modified Duke Criteria for the Diagnosis of IE (Modified from Ref. [10])**

***Definite Infective Endocarditis:***

**Pathological Criteria**

1. Microorganisms demonstrated by culture or histologic examination of a vegetation, an embolized vegetation, or an intracardiac abscess.
2. Pathologic lesions (vegetation or intracardiac abscess) confirmed by histology showing active endocarditis.

**Clinical Criteria**

1. Two major criteria
2. One major and three minor criteria
3. Five minor criteria

***Possible Infective Endocarditis:***

1. One major criterion and one minor criterion
2. Three minor criteria

***The Diagnosis of Infective Endocarditis is Rejected If:***

1. A firm alternative diagnosis is made
2. Resolution of suggestive IE manifestations with antibiotic therapy requires 4 days or less
3. No pathological evidence of IE is found at surgery or autopsy with antibiotic therapy administered for 4 days or less
4. Does not meet above criteria for possible IE

Echocardiography is used to identify any intracardiac findings associated with IE. A transthoracic echocardiogram is typically sufficient to identify cardiac abnormalities in young children with IE who weigh less than 60 kg. However, in children >10 years old, children who weigh >60 kg, and adults, or in those with prosthetic heart valves, a transesophageal echocardiogram is more sensitive to detect IE and to demonstrate complications such as valve root abscess [1]. A transesophageal echocardiogram is also recommended for children with a history of chest wall surgery or trauma and children with a history of congenital anomaly of the thoracic cage [► Call Out Box 10.4].

### 10.3.5 Management

Urgent evaluation and management of hemodynamic status is important in patients with suspected IE. Antimicrobial therapy is a mainstay of treatment, and bactericidal agents are preferred over bacteriostatic agents. Empiric antimicrobial therapy is based on the patient's age, risk factors and comorbidities, and local antimicrobial susceptibility patterns. Consultation with an infectious disease specialist should be considered. Antimicrobial selection should be adjusted based on results of susceptibility testing for the isolated pathogen. The AHA statement on IE provides

**Box 10.2 Definitions of Major and Minor Criteria Used in the Modified Duke Criteria from ► Box 10.1[a]**

**Major Criteria for the Diagnosis of IE:**

1. Positive blood culture for IE
   1. Typical microorganisms consistent with IE from two separate blood cultures:
      1. Viridans streptococci, *Streptococcus bovis*, HACEK group, *Staphylococcus aureus*
      2. Community-acquired enterococci or *Staphylococcus aureus* without primary focus
   2. Microorganisms consistent with IE from persistently positive blood cultures, defined as:
      1. ≥ 2 positive cultures of blood samples drawn >12 hours apart
      2. All of 3 or majority of ≥4 separate cultures of the blood (first and last drawn ≥1 hour apart)
   3. One positive blood culture for *Coxiella burnetii* or antiphase IgG antibody titer >1:800
2. Evidence of endocardial involvement
   1. Positive echocardiogram (TEE recommended in patients with prosthetic valves, rated at least "possible IE" by clinical criteria, or complicated IE) defined as:
      1. Oscillating intracardiac mass on valve or supporting structures, in path of regurgitant jets, or on implanted material in the absence of alternative anatomic explanation
      2. Abscess
      3. New partial dehiscence of prosthetic valve
   2. New valvular regurgitation (worsening or changing of pre-existing murmur not sufficient)

**Minor Criteria:**

1. Predisposing heart condition or injection drug use
2. Fever >38 °C
3. Vascular phenomena, major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, Janeway lesions
4. Immunologic phenomena: Glomerulonephritis, Osler's nodes, Roth spots, rheumatoid factor
5. Microbiological evidence: Positive blood culture but does not meet major criteria as above or serological evidence of active infection with organism consistent with IE

[a]Modified from references [1, 10]; TEE, transesophageal echocardiography

**Call Out Box 10.4**

**Diagnostic Approach to Infective Endocarditis**

- Diagnosis is based on clinical features, microbiological evidence, and echocardiogram.
- Multiple blood cultures should be drawn for patients in whom IE is suspected.
- A transesophageal echocardiogram may be necessary to detect IE in some children.

recommended antibiotic treatment regimens based on the pathogen [1].

In cases of IE caused by viridans streptococci, beta-lactam antibiotic therapy is recommended. Gentamicin is also recommended for at least the first 2 weeks in cases associated with prosthetic material or cases caused by a viridans streptococci that are relatively resistant to penicillin. Antimicrobial regimens for enterococcal endocarditis vary depending on the susceptibility to penicillin, gentamicin, and vancomycin. A beta-lactamase-resistant penicillin (oxacillin or nafcillin) is recommended for treatment of pediatric IE caused by methicillin-susceptible *S. aureus*, and vancomycin is recommended for IE caused by methicillin-resistant *S. aureus* (vancomycin susceptibility should be demonstrated). Gentamicin can be added to the regimen for the first 3–5 days in cases of *S. aureus* IE, but risks for aminoglycoside toxicity need to be considered. In cases of prosthetic valve endocarditis caused by *S. aureus*, rifampin should be added to the regimen, and gentamicin should be administered for the first 2 weeks of therapy. Valve replacement surgery may be indicated in prosthetic valve endocarditis, but considerations should include the infecting organism, size of the vegetation (if present), perivalvular involvement (typically more common in prosthetic valve cases), evidence of embolic phenomena, and presence of heart failure. Infectious diseases consultation is recommended to assist with antimicrobial treatment planning for all patients with IE especially in those with culture-negative IE.

Prolonged antimicrobial therapy (≥ 4 weeks) is recommended for most cases of IE, but the specific duration is based on the pathogen, presence of foreign material, and clinical course. Patients should be monitored for signs or symptoms of drug toxicity. Outpatient parenteral antimicrobial therapy can be considered for some children with IE who are low risk for complications after initial stabilization in hospital and documented clearance of bacteremia. A home monitoring plan is important to assess for adherence, medication side effects, and complications.

Complications of endocarditis can include heart failure, systemic embolic phenomena, splenic abscess, mycotic aneurysms (intracranial, intra-abdominal, or intrathoracic), and valvular perforation, rupture, or fistulae. Embolic phenomena can complicate the course of up to 50% of IE cases, especially in cases involving the aortic or mitral valve. The risk is highest during the first several days of treatment and in those individuals with mitral valve vegetations measuring greater than 1 cm. in length. While emboli may involve the lungs, coronary arteries, spleen, bowel, and extremities, central nervous system emboli are most common. More than 90% impact the distribution of the middle cerebral artery.

Surgical intervention is necessary for some patients with IE to reduce mortality and reduce the incidence of serious complications. In patients receiving chronic anticoagulation, transition to heparin therapy is recommended when the diagnosis of IE is established, in the event surgery is needed. The most common indications for surgery include severe congestive heart failure, presence of a large mitral valve vegetation with systemic emboli phenomena, and in cases complicated by perivalvular abscess, dehiscence, perforation, or rupture. Additionally, surgical intervention should be considered in cases with microbiologic treatment failure, defined as persistently positive blood cultures despite 1 week or more

**Box 10.3 Features of IE indicating the potential need for surgical intervention**

**Vegetation**
- Persistent vegetation after systemic embolization
  - Anterior mitral leaflet vegetation, especially >10 mm
  - ≥ 1 embolic event during first 2 weeks of antimicrobial therapy
  - ≥ 2 embolic events during or after antimicrobial therapy
- Increase in vegetation size after 4 weeks of antimicrobial therapy

**Valvular dysfunction**
- Acute aortic or mitral insufficiency with signs of ventricular failure
- Heart failure unresponsive to medical therapy
- Valve perforation or rupture

**Perivalvular extension**
- Valvular dehiscence, rupture, or fistula
- New heart block
- Large abscess or extension of abscess despite appropriate antimicrobial therapy

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of appropriate antibiotic therapy, in cases of left-sided disease caused by virulent gram-negative bacteria, or in cases caused by fungal pathogens. The decision to perform surgical intervention for IE cases is based on individual patient-specific factors as listed in ▶ Box 10.3. Early consultation with infectious diseases, cardiology, and cardiovascular surgery is important.

### 10.3.6 Prevention

Antibiotic prophylaxis for the prevention of IE in patients with underlying cardiac disease was common practice for many years. The efficacy of this practice was not well established by randomized clinical trials, and the majority of IE cases are not related to a preceding dental or medical procedure. The risk of adverse events associated with antibiotic exposure and the risk for development of antibiotic resistant organisms are increasingly recognized concerns related to antibiotic use. The AHA published a revised guideline on the prevention of infective endocarditis in 2007 [2]. The guideline emphasizes that maintaining good oral health and hygiene, which may reduce the incidence of bacteremia from daily activities such as toothbrushing, is more important to reduce the risk of IE than is antibiotic prophylaxis. The guideline also states that antibiotic prophylaxis for dental procedures is reasonable only for those patients with underlying cardiac conditions associated with the greatest risk for adverse outcome from infective endocarditis, including those with unrepaired cyanotic congenital heart disease, in the first 6 months following repair of congenital heart disease where prosthetic material was used or device placed, surgically corrected congenital heart disease with residual defect at the site or adjacent to foreign material, those with indwelling prosthetic valves, in heart transplant recipients with underlying valvulopathy, and in all who have had a prior bout of IE. Antibiotic prophylaxis to prevent IE with any other underlying congenital heart disease other than those listed above is not recommended.

**Case Study**

**Practical Examples**

**Case 1**

A previously healthy 26-year-old male was admitted to the hospital with 5-day history of fever and inability to bear weight on his right leg. At the time of admission, he had clinical sepsis, right knee pain and swelling, and left arm pain. Right knee pyogenic arthritis was diagnosed, and an incision and drainage procedure was performed. Methicillin-resistant *Staphylococcus aureus* grew from blood cultures within 12 hours of incubation. Blood cultures remained positive for 5 days despite the patient receiving vancomycin therapy with adequate serum trough levels. His left arm pain worsened, and he began to complain of new pain in his left leg. Magnetic resonance imaging revealed left humerus osteomyelitis and left tibia osteomyelitis with large subperiosteal abscesses and an associated pyomyositis. Incision and drainage procedures were performed, but bacteremia persisted. An echocardiogram revealed a 7 mm aortic valve vegetation. This case illustrates the importance of considering the diagnosis of IE in patients with disseminated *Staphylococcus aureus* disease, even in patients with structurally normal hearts. The presence of septic emboli, such as multifocal sites of osteomyelitis and soft tissue disease, is a clue to the diagnosis of an intravascular infection. A new cardiac murmur may also be present.

**Case 2**

A 2-year-old female with a history of a prosthetic aortic valve placement during infancy presents to cardiology clinic with 4-week history of fevers, fatigue, and poor appetite. She has lost weight during the illness and is less active than she was previously. Her family reports that they initially suspected multiple colds, but the persistence of the fevers led to her visit today. Physical examination reveals a pale, thin child with poor dentition, a systolic cardiac murmur, and splenomegaly. Multiple blood cultures are drawn, and all cultures are positive for *Streptococcus sanguinis* (a viridans group streptococcus). An echocardiogram reveals the presence of a vegetation of the prosthetic valve. This case illustrates the importance of considering IE in patients with prolonged fevers, especially patients with structural cardiac diseases or prior cardiac surgery.

### 10.3.7 Exercises

Please refer to the supplementary information section for answers to these exercises.

A 34-year-old previously healthy woman has had fever for the last week associated with headache and intermittent right arm numbness. She is initially thought to have a migraine variant with viral illness but on her second evaluation 2 days later, tachycardia with gallop rhythm and bilateral rales are noted. On laboratory evaluation, a normocytic anemia is present (hemoglobin 8.8 g/dL with normal platelets and white blood cell count), C-reactive protein is elevated to 8.6 mg/dL (normal <0.6 mg/dL), and the erythrocyte sedimentation rate is elevated at 67 mm/hour. An echocardiogram shows a 16 mm x 10 mm vegetation attached to the left atrial surface of the anterior mitral valve leaflet. *Streptococcus mitis* (a viridans group streptococcus) grows from two separate blood cultures.

? A magnetic resonance image of the brain is consistent with an embolic stroke. Surgical intervention is being considered for this patient. Which of the following factors is considered an indication for surgical intervention of her infected valve?

A. Anterior mitral valve leaflet vegetation, measuring more than 1 cm.
B. Vegetation size is unchanged after 5 days of appropriate antimicrobial therapy.
C. *Streptococcus mitis* has been isolated from blood cultures.
D. Fever was still present after 48 hours of appropriate antibiotic therapy.

? A patient who presents with septic shock and persistent *Staphylococcus aureus* bacteremia over 3 days has a normal transthoracic echocardiogram. Underlying factors are being considered to proceed to transesophageal echocardiogram (TEE). In which of the following conditions is TEE most likely to demonstrate findings consistent with infective endocarditis that were not appreciated on the transthoracic echocardiogram?

A. A 10-year-old with a bicuspid aortic valve
B. A 15-year-old with a prosthetic mitral valve
C. A 12-year-old with vertebral osteomyelitis but no history of congenital heart disease
D. A newborn with an unrepaired large ventricular septal defect

### 10.3.8 Summary

Infective endocarditis is an uncommon problem but important to recognize early since it is associated with significant morbidity and mortality. Most cases of infective endocarditis occur among those with underlying cardiac disease or prior cardiac surgery, but cases do occur without identifiable risk factors. Rheumatic heart disease remains an important risk factor for IE in developing countries. *S. aureus* and viridans group streptococci are the most common causes of IE. Due to the non-specific symptoms associated with subacute bacterial endocarditis, a delayed diagnosis is not uncommon. A high index of suspicion is needed in children with underlying congenital heart disease and in those who have undergone cardiac procedures requiring placement of foreign material. Unexplained fever and a new or significantly changed cardiac murmur are often the only early clues to the diagnosis. Endocardial involvement should be considered in those with acute onset of sepsis caused by *Staphylococcus aureus* and in those with bacteremia involving central venous catheters. Multiple blood cultures with appropriate volumes should be collected during the diagnostic evaluation of patients with suspected IE. Echocardiography is used to identify the presence of intracardiac findings associated with IE. A transesophageal echocardiogram may be necessary to detect these findings in some children and in many adults.

Recommendations from the American Heart Association guide diagnostic and treatment decisions for infective endocarditis; specialist consultation should be considered. Prolonged antimicrobial therapy is recommended for the treatment of infective endocarditis, although surgical intervention is indicated in some complicated cases. Prevention efforts should focus on the importance of oral hygiene and access to regular dental care. Recognition of those patients in whom antibiotic prophylaxis is generally recommended for dental procedures is important, although the indications for doing so now include a small minority of patients who are at the highest risk.

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# Infectious Myocarditis

## I Can't Breath and My Heart is Racing

*Matthew Egan*




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**Learning Objectives**

- Recognize common presenting signs and symptoms of myocarditis
- Understand clinical evaluation and testing for suspected myocarditis
- Review the common causes of myocarditis
- Discuss the prognosis for patients with myocarditis

## 11.1 Introduction to the Problem

Myocarditis is a rare but important cause of acquired heart disease. The diagnosis of myocarditis is challenging due to its varied presentation and multiple underlying causes. There are various laboratory and diagnostic tests used to aid in the diagnosis of myocarditis and to attempt to determine the responsible etiologic agent. The outcome in myocarditis is varied, ranging from full recovery to death or the need for heart transplant.

**Call Out Box 11.1: Evaluation of suspected myocarditis**

| Diagnostic tests | Laboratory tests |
|---|---|
| Chest radiograph | Complete blood count |
| Electrocardiogram | Comprehensive metabolic panel |
| Echocardiogram | C-reactive protein, erythrocyte sedimentation rate |
| Cardiac magnetic resonance imaging | Virus testing (culture, pathogen-specific PCR) |
| Catheterization with myocardial biopsy (limited use) | Troponin |
| | Other cultures, or nucleic acid amplification tests per clinical findings or unusual exposure history |

## 11.2 Definitions

**Myocarditis** - inflammatory disease of the myocardium or heart muscle

**DCM** - dilated cardiomyopathy

**Cardiomegaly** - enlarged heart

**ECMO** - extracorporeal membrane oxygenation

**VAD** - ventricular assist device

## 11.3 Basic Concepts

The diagnosis of myocarditis is challenging for many reasons. There are a wide range of symptoms that are demonstrated, and these will vary significantly between patients. The clinical presentation varies based on the effects of myocarditis on the ventricular function of the heart. This can range from normal ventricular function to a mild decrease in the function to a severe dilated cardiomyopathy with signs of low output cardiogenic shock.

A high index of suspicion is required to make the diagnosis of myocarditis since it is uncommon and often, initially, mimics more routine illnesses. Patients are often evaluated multiple times prior to being diagnoses with myocarditis. One study showed that 84% of patients required more than one visit within 2 weeks of the eventual diagnosis and many were seen multiple times [1]. An initial diagnosis of a more common ailment, such as pneumonia or an upper respiratory infection, is quite typical. There is a bimodal distribution of increased frequency of myocarditis, with peaks in prevalence less than 2 months of age and during adolescence [2]. Infants often present with tachypnea, poor feeding, vomiting, and lethargy, and some may have a fever [1]. In addition, older children and adults typically complain of symptoms common to heart failure such as shortness of breath, orthopnea, or cough (secondary to pulmonary edema). Chest pain as a prominent complaint is not typical.

The physical examination of patients with myocarditis is helpful in securing the diagnosis. Patients who still have good ventricular function will often have normal physical examination findings. Patients with decreased ventricular function, however, often look distressed, with evidence of increased work of breathing. The cardiac examination may have a gallop rhythm, with an audible third heart sound. There may be a holosystolic murmur if significant mitral regurgitation is present due to a dilated cardiomyopathy. It is also very important to perform a thorough abdominal examination because hepatomegaly is present in patients with myocarditis at least half of the time [1]. The hepatomegaly is secondary to venous congestion related to poor cardiac output.

Diagnosing myocarditis is especially difficult during the winter season when there are large volumes of patients with similar presenting complaints related to viral upper respiratory symptoms. It is during this time when vigilance and increased clinical suspicion is required. Infants and children who do not improve with typical respiratory therapy management or whose clinical presentation worsens with fluid resuscitation should be considered for an alternate diagnosis, such as myocarditis.

There are numerous laboratory and diagnostic tests that can be beneficial in establishing a diagnosis of myocarditis, although there is not a single test used to diagnose it (▶ Call Out Box 11.1). A chest radiograph is usually abnormal in patients with significant myocarditis. The chest radiograph can demonstrate cardiomegaly and/or pulmonary edema. An electrocardiogram (EKG) is also beneficial. The EKG most commonly demonstrates sinus tachycardia. There can be other non-specific changes such as ST or T wave abnormalities [1]. Some patients will have evidence of atrioventricular block, bundle branch block, or arrhythmias, such as premature ventricular contractions or ventricular

tachycardia [3] . Children with cardiomegaly due to dilated and poorly functioning ventricles can also have evidence of left ventricular hypertrophy on the EKG. Together, the chest radiograph and the EKG are good, readily available initial tests when considering the diagnosis. An echocardiogram is an excellent diagnostic tool and the next test to consider when there are abnormalities on the EKG or chest radiograph supporting the clinical suspicion that the patient has myocarditis. The echocardiogram is able to delineate the anatomy of the heart to ensure that there is no underlying form of pre-existing congenital heart disease. It is also able to provide quantitative information regarding the ventricular function. Patients with myocarditis can have decreased ventricular function, mitral regurgitation, pulmonary hypertension, and effusions noted on echocardiography. There are also times that the echocardiogram can demonstrate evidence of a thrombus within the ventricles secondary to the poor cardiac function. Some patients with milder forms of myocarditis have normal echocardiograms.

An initial laboratory evaluation should be performed when suspecting myocarditis in coordination with the diagnostic tests discussed above. This should include basic laboratory tests such as a complete blood count (CBC) and a comprehensive metabolic panel (CMP). The CMP is important to evaluate renal and hepatic markers to ensure that there is no evidence of end-organ dysfunction secondary to poor cardiac output. A C-reactive protein and/or erythrocyte sedimentation rate are helpful in this situation to gauge the amount of any residual inflammation. Viral cultures and more sensitive viral diagnostic tests, such as polymerase chain reaction, should be considered when searching for the underlying cause. If there are clinical findings or historical risk factors supportive of any specific viral, bacterial, fungal, or parasitic etiology, then targeted testing for those should be performed as well since the list of pathogens that can trigger myocarditis is extensive.

The role of blood troponin assays in the evaluation of patients with suspected myocarditis has been controversial. Troponin is a component of cardiac muscle that is released into the blood when there in injury to heart muscle. Troponin T and troponin I are two subunits that are often checked clinically. Troponin is a very sensitive indicator of myocardial cell injury, which can occur with myocarditis. Therefore, due to its high sensitivity and negative predictive value, troponin is a good screening test to help exclude myocarditis [4]. Troponin release is not specific to myocarditis. It is elevated in many other situations such as coronary artery disease, heart failure, arrhythmia, and even following significant exercise. The troponin I level has also been shown to correlate with the ventricular function on echocardiogram [5].

Cardiac magnetic resonance imaging (MRI) has emerged as a very important test in the diagnosis of myocarditis. Cardiac MRI can aid in the diagnosis in multiple ways. First, cardiac MRI is an excellent test to provide functional measurements of ventricular function and to measure the size of the ventricles. As opposed to other tests, such as echocardiography, cardiac MRI also allows for characterization of the myocardial tissue. It is able to evaluate for the initial signs of myocarditis, such as parenchymal edema and inflammation. It is also able to evaluate for necrosis and fibrosis after the injection of the contrast gadolinium by looking for myocardial delayed enhancement. The majority of patients with myocarditis will have abnormally delayed enhancement [6]. The patchy, subepicardial pattern of abnormal myocardial delayed enhancement in myocarditis is different than in other processes, such as ischemia [7]. The late delayed gadolinium enhancement has been shown to correlate with increased troponin levels related to the myocardial injury. Also, patients with a larger extent of delayed enhancement had a worse outcome with more adverse events [8]. Despite the many advantages, cardiac MRI has limitations as well. The study may require anesthesia in younger patients who cannot cooperate with the study and require transporting the patient to the magnet, which may not be safe for patients who are hemodynamically unstable.

Cardiac catheterization may also be considered when evaluating a patient for myocarditis. The catheterization provides hemodynamic information about the pressures in the heart which can help guide the prognosis. The catheterization also provides the opportunity to perform an endomyocardial biopsy. Biopsy tissue can be used for histologic analysis and viral PCR testing in an attempt to determine the underlying etiology [9]. Due to the patchy nature of myocarditis affecting the heart, the biopsy may not be a sensitive test. As opposed to the other noninvasive tests, the catheterization and biopsy have the added risks of complications, such as arrhythmia or perforation. These complications are uncommon, but when combined with the low sensitivity yield of the test, it may be difficult to justify its use [9].

## 11.4 Differential Diagnosis

Another aspect that makes the diagnosis of myocarditis difficult is the numerous other causes of cardiac dysfunction that can present in a similar manner. Distinguishing the effects of myocarditis from an inherited or idiopathic dilated cardiomyopathy is often very difficult. Patients with sepsis can present with myocardial dysfunction similar to that seen during infectious myocarditis. Noninfectious etiologies should always be considered in the differential diagnosis. Severe hypothyroidism or hyperthyroidism and adrenal hormone-producing tumors (pheochromocytomas) can present with heart failure symptoms with associated signs of temperature instability suggesting, at first look, that the patient has an infection. Children with certain metabolic syndromes may present primarily with cardiac dysfunction. It is also important to rule out structural congenital heart disease, such as a coarctation of the aorta, in an infant. There also can be anomalies of the coronary arteries, such as anomalous left coronary artery from the pulmonary artery which can present in the first couple of months of life with left ventricular dysfunction and heart failure. Arrhythmia is another important consideration when an infant or child

presents with heart failure. Younger infants with supraventricular tachycardia may not demonstrate any symptoms until cardiac dysfunction develops, which often occurs many hours or days after the onset of the tachycardia. In older children and adults, incessant atrial tachycardia can also present with heart failure [9, 10].

## 11.5 Pathogens That Cause Myocarditis

There are numerous viral and nonviral causes of triggering the immune cascade that ultimately leads to clinical myocarditis (▶ Call Out Box 11.2). It is not unusual, even after an extensive microbiologic diagnostic evaluation, for the underlying cause to remain unknown [1]. Efforts can be made to culture viruses from the blood, respiratory secretions, urine, or stool, but in each circumstance, a positive result is only suggestive of causality. Efforts to identify virus-specific nucleic acid from the same biologic samples offer a much more sensitive technique compared with culture, with the same difficulty in determining causality [11].

The most common etiologies of infectious myocarditis have shifted over time [9]. One of the most commonly identified agents are pathogens in the enterovirus family. Coxsackie A, coxsackie B, echoviruses, and several of the numbered enteroviruses have all been associated with myocarditis. These members of the enterovirus family were initially described as the most frequent viruses to cause myocarditis and remain an important etiology. Adenoviruses were found to be an important underlying cause during several studies performed during the 1990s and early 2000s [12]. Even more recently, human herpes virus 6 (HHV6) and parvovirus B19 have been implicated with increased frequency [13]. Cytomegalovirus (CMV), Epstein-Barr virus (EBV), influenza A, and respiratory syncytial virus (RSV) are other common viral pathogens that have also been associated with myocarditis. The term "infectious myocarditis" is often used synonymously with "viral myocarditis," because viruses cause the majority of cases. Much less commonly myocarditis can be caused by any of the bacterial, fungal, and parasite pathogens listed in ▶ Call Out Box 11.2.

Myocarditis can also be caused by noninfectious, inflammatory conditions such as Kawasaki disease, acute rheumatic fever, and systemic lupus erythematosus (SLE). Toxins and drug reactions can also be implicated in the development of myocarditis with dilated cardiomyopathy. The extremely wide range of potential pathogens and long list of possible noninfectious causes of myocarditis reflect the need for a detailed patient history and thorough evaluation to determine the underlying cause in an individual patient. Since the cardiac manifestations of myocarditis are similar despite the underlying etiology, the details of the history of present illness, any associated past medical history, including travel or known exposures to unusual agents, and the patient's noncardiac signs and symptoms will most likely offer the best clues as to the underlying cause. A broad diagnostic evaluation is otherwise necessary.

## 11.6 Management

The management of patients with myocarditis is patient specific. If there is an identified, treatable viral, bacterial, fungal, or parasitic infection identified, then the appropriate anti-infective treatment should be provided. While specific anti-infective therapy is available for each of the bacterial, fungal, and parasitic causes of myocarditis listed in ▶ Call Out Box 11.2, of the viruses listed, specific antiviral therapy is

**Call Out Box 11.2: Infectious causes of acute myocarditis**

| Viruses | | Rare: bacteria | Rare: fungi | Rare: parasites |
|---|---|---|---|---|
| Most common | Common | | | |
| Enteroviruses- including coxsackie A, coxsackie B, and echoviruses | Human herpes virus 6 | *Borrelia burgdorferi*[a] | *Coccidioides immitis* | *Trypanosoma cruzi*[b] |
| | Influenza A | *Mycoplasma pneumonia* | *Candida* species | *Toxocara canis* |
| Adenoviruses | Epstein-Barr virus | *Mycobacterium tuberculosis* | *Histoplasma capsulatum* | *Trichinella spiralis* |
| Parvovirus B19 | Cytomegalovirus | *Neisseria meningitidis* | | *Schistosoma* species |
| | Respiratory syncytial virus | *Actinomyces* species | | |
| | | *Rickettsia rickettsii* | | |

[a] *Borrelia burgdorferi* is the bacterial cause of Lyme disease. During early disseminated Lyme infection, carditis is a regular finding, typically presenting as first degree heart block. Moderate to severe myocarditis can occur but is rare. See also the chapter on Lyme Disease (▶ Chap. 32)
[b] *Trypanosoma cruzi* is a protozoan parasite that causes Chagas disease. The infection is endemic to most of South and Central America where it remains the most common cause of acute and chronic myocarditis

only available for the treatment of influenza and cytomegalovirus. Even after performing a broad diagnostic evaluation, a specific infectious etiology is only occasionally identified, leaving supportive care as the primary therapy in the majority of cases.

A large multicenter database review study demonstrated that 80% of pediatric patients who are hospitalized with myocarditis are admitted to intensive care [2]. Intubation and mechanical ventilation is often necessary during the acute phase of the illness. Atrial and ventricular arrhythmias occur frequently in patients with acute heart failure, often leading to significant morbidity. If there is evidence of poor cardiac output with hypotension or poor perfusion, inotropic support is initiated. The choice of inotrope used as the initial therapy varies among centers [2]. Milrinone, dobutamine, epinephrine, dopamine, and norepinephrine are all used to support cardiac output and are, at times, used in combination. Milrinone is often effective in these patients based on the mechanism of action as a phosphodiesterase inhibitor. The side effect profile can favor this as well compared to catecholamines, which can increase myocardial oxygen demand and afterload by increasing systemic vascular resistance [14]. If mechanical ventilation and inotropic support does not adequately improve the cardiac output, then patients will require mechanical support. For many years, mechanical support meant extracorporeal membrane oxygenation (ECMO). Ideally, the procedure provides adequate oxygen to the tissues in the body while allowing for recovery of myocardial function. Recently, there has been an increase in the utilization of ventricular assist device (VAD) for both short-term and longer-term cardiac dysfunction [2, 9]. The mechanical support can be weaned and removed as ventricular function improves or can be used as a bridge to cardiac transplantation.

Other treatment options for myocarditis are also sometimes used. Intravenous infusions of pooled human immunoglobulin IgIV as adjunctive therapy for the treatment of myocarditis remains controversial [15]. Intravenous glucocorticoid administration has also been used in many situations. Several follow-up studies have failed to demonstrate any clear benefit of using either of those therapeutics in the treatment of myocarditis [16]. Despite the lack of any clear benefit, both IgIV and systemic glucocorticoids are frequently used in pediatric patients with acute myocarditis due to the relatively low risk of serious side effects and the theoretical that a subset of patients might benefit from their use [2].

## 11.7 Outcome

The outcome of patients who are diagnosed with myocarditis is quite variable. A portion of the patients will have a complete recovery with no long-term problems. There is another group of patients who will recover from the acute illness but have a dilated cardiomyopathy with long-term ventricular dysfunction requiring frequent follow-up visits with cardiologists and medical management for ongoing congestive heart failure. Some patients will have severe cardiac dysfunction leading to poor cardiac output and arrhythmias that can only be corrected or improved with cardiac transplantation [17].

It is extremely difficult to predict the outcome for a specific patient at the time of presentation. Intuitively, children who require more significant supportive care with inotropes or mechanical circulatory support are more likely to have a worse outcome. According to the recent multicenter study by Ghelani, 7% of the total patients reviewed died due to the myocarditis and another 4% received a heart transplantation. These percentages increased to 16% and 24% when the patient was supported with mechanical circulatory support [2]. The numbers also demonstrate that the majority of children, even those that require ECMO or a VAD, will survive.

## 11.8 Practical Example

A 10-month-old previously healthy female was admitted to the pediatric service with symptoms of poor feeding and increased work of breathing. She had been evaluated 2 weeks prior to the visit for an upper respiratory infection. At the time, a nasopharyngeal swab was collected that tested positive by PCR for adenovirus and enterovirus. After being admitted to the inpatient unit, she developed worsening respiratory status and hypotension. She received 60 mL/kg of IV fluid boluses and was transferred to the pediatric intensive care unit. She had respiratory failure shortly after the transfer and was intubated. She then had evidence of a wide complex arrhythmia consistent with ventricular tachycardia. She received the anti-arrhythmic medication amiodarone. She had an echocardiogram that demonstrated severely depressed left and right ventricular systolic function with mitral regurgitation and evidence of pulmonary hypertension (Fig. 11.1a, b). The coronary artery origins were demonstrated to arise from the normal locations. She was treated with milrinone and dopamine for inotropic support. Her laboratory evaluation showed a severe metabolic acidosis that was not improving with the therapy so she was placed on venoarterial ECMO. At this time, her acidosis started to improve, and her hemodynamics became stable.

In the following days, the patient received IgIV and intravenous glucocorticoids. She developed acute renal failure requiring dialysis. She did not tolerate weaning from mechanical circulatory support, and her ventricular function remained severely depressed several days later. She was then transported to the cardiac catheterization lab while on ECMO. She had a transseptal puncture of the atrial septum and subsequent placement of a stent through the atrial septum in an effort to decompress the left side of the heart to allow for better recovery (Fig. 11.1c). Her function subsequently improved, and she was weaned off of ECMO 1 week later. She was transitioned from the intravenous inotropes to oral medications.

She gradually recovered but had persistent feeding issues which led to the placement of a g-tube for improved nutrition. Her kidney function returned to normal. She was grad-

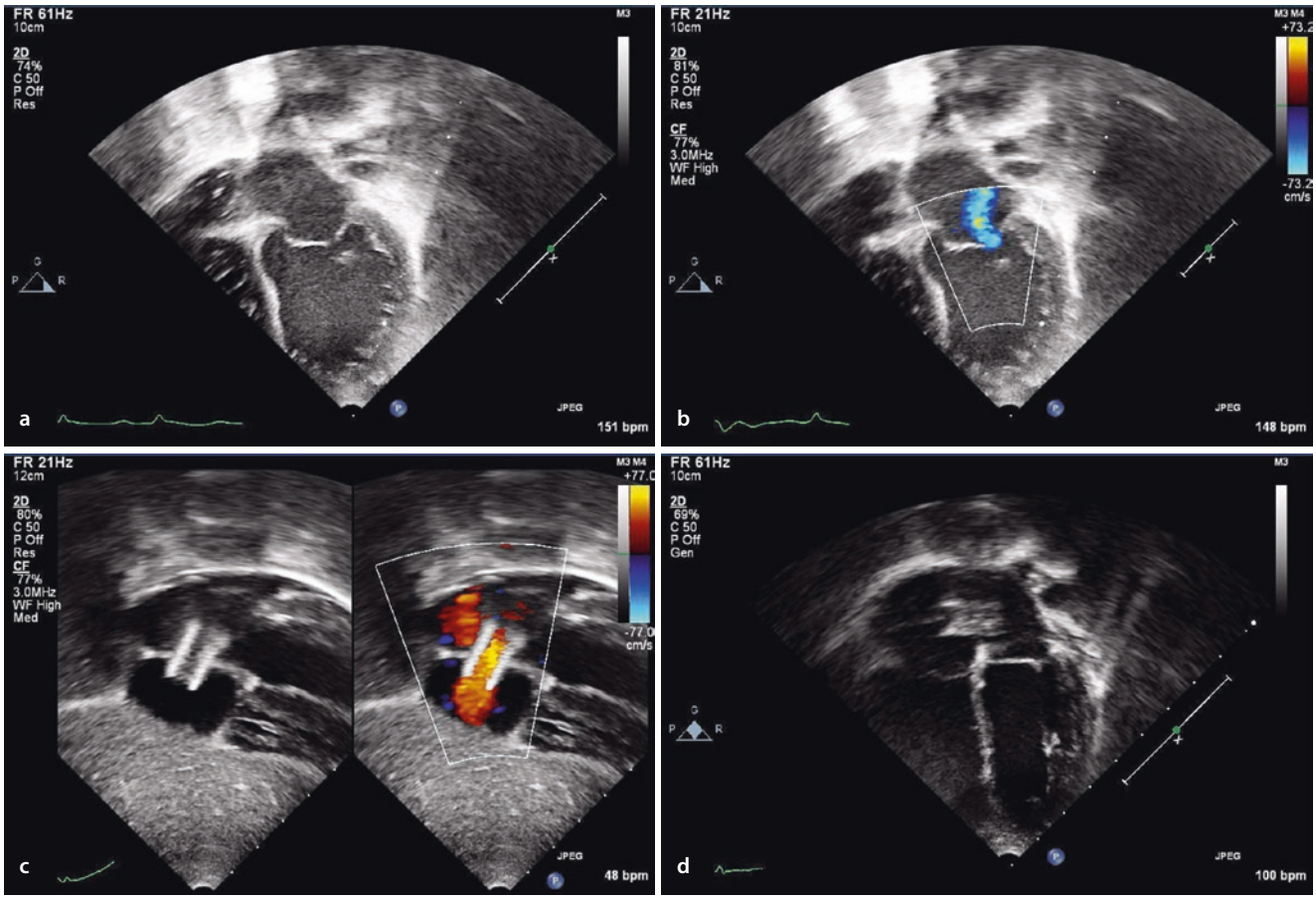


**Fig. 11.1** Echocardiogram images from practical example. **a** Initial echocardiographic image at presentation with enlarged left atrium and an enlarged left ventricle with rounded appearance, **b** Initial echocardiographic image with color Doppler showing severe mitral regurgitation, **c** Echocardiographic image of the atrial stent placed to decompress the left side of the heart with color flow through the stent from the left atrium to right atrium, **d** Echocardiographic image after recovery with normal left ventricular size, and the atrial stent still in place

11

ually weaned off her cardiac medications over the next several months (Fig. 11.1d). A year later, she had open heart surgery to remove the atrial septal stent that was placed during the acute illness, and the resulting atrial septal defect was patch closed. She recovered well from the operation and has been doing well as an outpatient with a good activity level.

## 11.9 Exercises

Please refer to the supplementary information section for answers to these exercises.

| Complications | Etiologies |
|---|---|
| 1. Late gadolinium enhancement | a. Common cause of viral myocarditis in the United States |
| 2. Echocardiogram | b. Portable ultrasound test that defines cardiac anatomy and ventricular function in numerous situations, including suspected myocarditis |
| 3. Endomyocardial biopsy | c. Cardiomegaly and pulmonary edema are common findings on this test in cases of myocarditis |
| 4. Coxsackie viruses | d. Patchy, subepicardial areas associated with myocarditis |
| 5. Ventricular assist device | e. Cause of Chagas disease and myocarditis in South America |
| 6. Milrinone | f. Performed less frequently in myocarditis but typically safe in experienced centers |
| 7. Chest radiograph | g. Often used as a first-line inotrope to support ventricular function |
| 8. *Trypanosoma cruzi* | h. Mechanical circulatory support that can be used until function returns or transplantation |

1. A 6-month-old presents to the emergency department after a week of upper respiratory symptoms. Of the following options, which physical examination finding is most concerning for poor cardiac output secondary to myocarditis?
   a. Tachycardia
   b. Transmitted upper airway sounds
   c. Hepatomegaly
   d. Systolic ejection murmur
   e. Rhonchi

2. A 14-year-old is suspected to have viral myocarditis. He presents with dyspnea on exertion after a recent upper respiratory tract infection. His laboratory test results show an elevated troponin and elevated C-reactive protein. His electrocardiogram demonstrates sinus tachycardia with non-specific ST-segment changes. His echocardiogram demonstrates low normal left ventricular systolic function with normal appearing coronary artery origins. Which noninvasive test would allow for further characterization of his ventricular function in an effort to confirm a diagnosis of myocarditis?
   a. Cardiac magnetic resonance image performed with gadolinium contrast
   b. Cardiac computer tomography scan
   c. Cardiac catheterization with endomyocardial tissue biopsy
   d. Exercise stress test

3. Which statement about the utility of troponin in the evaluation of a patient for myocarditis is true?
   a. A positive troponin is diagnostic for myocarditis
   b. There is no relationship between an elevated troponin and the affected area of the myocardium
   c. A normal troponin level makes the diagnosis of myocarditis unlikely
   d. Troponin assays are not helpful due to the time that it takes for results to become available

## 11.10 Summary

Infectious myocarditis occurs infrequently. It can be difficult to diagnosis due to its non-specific presenting signs and symptoms, as well as the lack of a single specific diagnostic test. A high index of suspicion needs to be maintained to identify these patients so an appropriate diagnostic evaluation and management plan can be initiated. There are numerous infectious and noninfectious causes of myocarditis. Often, no underlying inciting organism is defined. The initial care is supportive. Further research is required to further demonstrate the inflammatory process that causes myocarditis as this could lead to more specific diagnostic tests and therapeutic options. Numerous studies have shown that the majority of patients diagnosed with acute myocarditis will survive, although some will have long-term morbidity due to the development of a dilated cardiomyopathy.

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### Further Reading

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# Acute Rheumatic Fever

## Licks the Joints, But Bites the Heart

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**Learning Objectives**

- Learn the historical aspects of rheumatic fever
- Understand the epidemiology, pathogenesis, and etiology of rheumatic fever
- Appreciate the clinical approach, diagnostic criteria, and management strategies for rheumatic fever

**Call Out Box 12.1**
Acute rheumatic fever and rheumatic heart disease remain significant problems in low- and middle-income countries and among certain populations in higher-income countries.

## 12.1 Introduction to Acute Rheumatic Fever

### 12.1.1 Historical Perspective

In the early twentieth century, ARF was a major cause of morbidity and mortality in children, adolescents, and young adults. Many cities in the USA had dedicated centers that were established specifically for the care of these patients. At the time, antibiotics were not yet available, and efforts for supportive treatment were ineffective. Several early studies confirmed the role of *Streptococcus pyogenes* (group A streptococcus) as the instigating pathogen responsible for the disease process. During the Second World War, cases of ARF were rampant among military forces. The importance of antibiotic therapy for streptococcal pharyngitis became well appreciated soon after their discovery. During the post-penicillin era, a steady decline was noted in both the incidence of and mortality from ARF.

Even though this entity has been known and studied for a century, the precise pathophysiology remains unknown. The seminal "Jones criteria," credited to Dr. T.D. Jones, based on studies of large numbers of afflicted individuals, are still used today to confirm the diagnosis [1–3].

## 12.2 Epidemiology

The epidemiology of ARF and rheumatic heart disease (RHD) has evolved quite dramatically since the first descriptions of the illness. In general, the epidemiology of ARF and RHD is primarily of historic context in the USA and other developed countries; but this is not the case in the developing world. Presently, the global burden of RF/RHD is thought to be grossly underestimated. As of 2010, it was estimated that ARF and RHD could account for as many as 15.6 million cases and 200,000 deaths annually. A particularly notable aspect of the disease epidemiology is its striking discordance between developed and developing countries. In fact, even in high-income countries, there are wide disparities among populations. One of the most obvious examples of this is seen in Australia. According to a 2013 government report, the prevalence of RHD among the indigenous population was 26 times higher than the general population [4]. In the USA, even though the overall rates of ARF and RHD have declined dramatically over the last century, individuals from the state of Hawaii and from American Samoa continue to experience rates of disease that are two to three times higher than the general population [5].

The reason(s) for the ongoing discrepancy in disease rates between developed and underdeveloped areas of the world are not well understood but are most likely multifactorial involving circumstances associated with socioeconomic differences, variations in hygiene practices, accessibility to antibiotics, differences in housing conditions, and other factors. The discrepancy in rates of disease seen globally closely mirrors disparities in health care seen across nations of the world [4–8] [► Call Out Box 12.1].

*Streptococcus pyogenes* (group A streptococcus) infection triggers the events that lead to ARF and RHD, yet the vast majority of infections caused by these bacteria do not lead to rheumatic complications. A combination of host and pathogen factors are required to trigger the series of immunologic events ultimately responsible for the development of ARF and for the differences in the specific manifestations of the inflammatory condition seen. Group A streptococci are a heterogeneous group of bacteria whose epidemiologic patterns have been well studied. Strain to strain variation is well appreciated, based largely on differences in the bacterial M protein [9, 10].

Streptococcal pharyngitis, impetigo, and cellulitis are very common infections with higher numbers of cases seen during the winter and spring months [11]. The US Centers for Disease Control and Prevention carefully tracks cases of severe invasive group A streptococcal disease such as bacteremia and necrotizing fasciitis, but cases of pharyngitis and impetigo are not reportable.

## 12.3 Basic Concepts

### 12.3.1 Pathogenesis

Dr. Walter Butler Cheadle, a British pediatrician, is credited with the first comprehensive account of AFR and its association with tonsillitis, in 1889 [12]. Several decades before that, in 1812, Dr. W.C. Wells described the link between ARF and carditis. By the year 1900, a clear association between "infection" and ARF had been described [13]. The etiologic role of the group A streptococcus as the trigger for this condition has been studied extensively ever since [14, 15]. Efforts to identify pathogen-specific determinants responsible for triggering the development of ARF began in the 1930s [9], yet the precise pathogenic mechanism(s) have remained elusive.

It is well appreciated that epidemics of ARF are preceded by epidemics of streptococcal pharyngitis. The consistent finding of elevated serum concentrations of antistreptococcal antibodies in the blood of patients with ARF is certainly

helpful diagnostically but was also an important clue in appreciating the role of the immune response in the pathogenesis of the disease [15, 16]. The observation that ARF only develops following antecedent group A streptococcal infection of the pharynx (and not the skin) remains unexplained.

*S. pyogenes* are gram-positive cocci that can reside on the skin and in the throat of healthy people. Colonized individuals become susceptibility to infection when the pharyngeal mucosa or break is disrupted or when they are exposed to and acquire a new strain. Group A streptococci are associated with infections of the skin and soft tissues ranging from impetigo to necrotizing fasciitis, exudative tonsillitis, pharyngitis, pneumonia, and bacteremia. Hematogenous seeding of the bones, joints, or meninges are all well-known suppurative complications of bacteremia. Nonsuppurative complications of group A streptococcal infections include ARF, post-streptococcal glomerulonephritis, and post-streptococcal reactive arthritis [15, 17].

ARF is widely considered a delayed autoimmune response following group A streptococcal pharyngitis. The most commonly held view, based on decades of study, is that the acquired humoral and cell-mediated immune responses to the infection cross-react with epitopes expressed on host tissues. The concept of molecular mimicry, i.e., similarities between the antigens expressed by various pathogens with those expressed by host tissues, continues to be an area of intense investigation. The most widely implicated streptococcal virulence factor in the molecular mimicry paradigm is the bacterial M protein [15, 16, 18]. The individual variation in the intensity of the host-specific immune responses to M proteins and the recognized variations in the M proteins between strains of group A streptococci explain, in part, why only some individuals develop ARF following streptococcal pharyngitis and why the manifestations of ARF vary from one patient to the next. Repeated bouts of group A streptococcal pharyngitis are thought to be an essential trigger for the development of ARF. On the other hand, individuals who harbor GAS in the pharynx ("carriers") are not at increased risk of developing ARF. The reasons for these observations remain unknown [15, 16, 19] [▶ Call Out Box 12.2].

The French doctor Ernest-Charles Lasegue made the following evocative statement in the 1880s: "Pathologists have long known that rheumatic fever licks at the joints, but bites at the heart" [20]. Subsequently, Dr. T.D. Jones characterized the clinical manifestations of ARF and created the eponymous Jones criteria, which have been in use for more than 70 years. Since their inception, the Jones criteria have been validated extensively. The most recent iteration of the "modified" Jones criteria was updated in 2015.

**Call Out Box 12.2**
Acute rheumatic fever is a nonsuppurative complication of group A streptococcal pharyngitis. The precise mechanism(s) by which this process is triggered remains unclear.

Patients who have signs, symptoms, and laboratory findings sufficient to fulfill the Jones criteria are confirmed to have ARF. Culture, serologic evidence of a preceding infection with group A streptococcus, or a recent clinical diagnosis of scarlet fever is considered essential, unless a patient presents with carditis or Sydenham's chorea. In addition, confirmation of ARF requires that the patient meets either two major criteria or one major and two minor criteria, for the diagnosis [◘ Table 12.1] [8, 21, 22]. Generally, the manifestations of rheumatic fever develop between 2 and 4 weeks following streptococcal pharyngitis. ARF is not restricted to the pediatric population, but cases are most common in children who are between the ages of 5 and 15 years [23, 24].

Jones' major diagnostic criteria include carditis, arthritis, Sydenham's chorea, erythema marginatum, and subcutaneous nodules. Minor criteria include fever, prolonged PR interval on EKG, arthralgias, and elevation in either the erythrocyte sedimentation rate or the C-reactive protein. The 2015 update of the Jones criteria introduced important changes. For the first time, the criteria were modified based on the risk of the population where the case occurs (a low-risk population is defined as one wherein ARF incidence is ≤2 per 100,000 school-aged children or the overall prevalence of rheumatic heart disease is ≤1 per 1000 population years.) Improvements in echocardiography have allowed the addition of subclinical or clinically inapparent carditis, as a major criterion. The audible presence of a new murmur is no longer required if the echocardiogram reveals evidence of carditis. Another change included with the new update is the acknowledgement that reliance on migratory polyarticular arthritis as a major criterion does not encompass other forms of joint manifestations that can be seen in patients with ARF including monoarticular arthritis and polyarthralgia. The 2015 guidelines also specifically mention the increased risk for recurrence of ARF in those individuals with a prior history of ARF/RHD and state that in this situation, either two major, one major and two minor, or three minor criteria with evidence of prior group A streptococcal infection are sufficient to fulfill the Jones criteria [8, 22]. The individual

**◘ Table 12.1** Major and minor diagnostic criteria for acute rheumatic fever in low-risk populations

| Supportive evidence of an antecedent group A streptococcal infection is required | |
|---|---|
| **Major criteria** | **Minor criteria** |
| Carditis[a]<br>Polyarthritis<br>Chorea<br>Erythema marginatum<br>Subcutaneous nodules | Fever ≥ 38.5 °C<br>Polyarthralgia in the absence of arthritis<br>ESR >60 mm/hr and/or CRP ≥ 3 mg/dL<br>Prolonged PR interval on EKG in the absence of carditis |

[a]Based on clinical and/or echocardiographic criteria

manifestations of rheumatic fever and rheumatic heart disease each have their differential diagnoses, especially in cases where the diagnosis of ARF is not clearly evident on initial presentation. Obtaining a thorough history, performing a meticulous physical examination, and methodical review of relevant laboratory and other clinical data are crucial in arriving at the correct diagnosis.

## 12.4 A Closer Look at the Major Diagnostic Jones Criteria

### 12.4.1 Carditis

Rheumatic fever involves multiple organs and tissues, but the most significant long-term consequences are related to the cardiac involvement. ARF "licks the joints but bites the heart." The clinical manifestations depend on the layers of cardiac tissue affected. Involvement of myocardium, endocardium, and pericardium together is referred to as "pancarditis," but most commonly it is the endocardium (valves) that is disproportionately affected. Carditis may be detected clinically by the presence of a new murmur, an unexplained elevation in heart rate, the presence of a dysrhythmia, or emergence of congestive heart failure. With valvular involvement, the most common findings on auscultation murmurs are a systolic murmur of mitral regurgitation heard at the apex, and a diastolic murmur of aortic regurgitation heard best along the upper left sternal border. Involvement of the tricuspid and pulmonic valves is less common [23, 24]. The differential diagnosis for rheumatic carditis is very broad and includes bacterial endocarditis, Kawasaki disease, undiagnosed congenital valvular disease, other autoimmune diseases such as systemic lupus erythematosus (SLE), sarcoidosis, and others [25].

### 12.4.2 Articular Manifestations

The archetypal joint finding in ARF is large joint migratory polyarthritis; however, other forms of joint involvement can also be seen including monoarticular arthritis and polyarthralgia. A diagnosis of arthritis required the objective presence of acute inflammatory changes in the joint (red, hot, swelling, pain, loss of function). The term arthralgia is used to describe the presence of pain without other signs of inflammation. Arthritis is very common in ARF, seen in approximately 75% of those afflicted. The differential diagnosis is again quite broad and includes septic arthritis, Lyme arthritis, inflammatory arthritis (including Still's disease, rheumatoid arthritis, systemic lupus erythematosus), and crystal arthropathy. Postinfectious reactive arthritis can also be seen following streptococcal pharyngitis. When present, it is important to look carefully for the potential presence of other major and minor diagnostic Jones criteria. If they are absent, the patient more likely has isolated postinfectious arthritis and not ARF [6, 23].

### 12.4.3 Chorea

First described by Dr. Thomas Sydenham in the 1600s, Sydenham's chorea is a movement disorder characterized by abnormal uncontrolled writing, sometimes associated with mood disturbances. Symptoms typically begin several months after the initial group A streptococcal infection. Their uncontrollable nature can be extremely distressing. Patients suffer from sudden, unprovoked, and purposeless movements of the extremities sometimes accompanied by muscle weakness, mood changes, or obsessive compulsive behavior. The severity of the neurologic symptoms ranges from mild to severe. The abnormal movements may resolve spontaneously after several weeks or months. More long-lasting chorea, leaving patients with permanent disability, has also been described [23, 26]. The differential diagnoses for Sydenham's chorea include movement disorders associated with other autoimmune diseases, atypical seizure disorders, cerebrovascular accidents (CVA), and degenerative causes of chorea such as Huntington's disease [6].

### 12.4.4 Erythema Marginatum

Erythema marginatum is the classic dermatologic manifestation of ARF, but it only occurs in 10–15% of affected patients. The typical presentation is that of multiple macular lesions that spread in a centrifugal (from the trunk out to the extremities) fashion. The face, palms, and soles are spared. It does not itch. The rash appears early in the disease process and may wax and wane. The serpiginous "margins" seen with the rash are quite characteristic, but a small number of other skin eruptions occasionally mimic erythema marginatum, including erythema chronicum migrans (the rash of early localized Lyme disease), the rash of Still's disease, atypical cases of erythema multiforme, urticaria, and some viral exanthems [6, 23].

### 12.4.5 Subcutaneous Nodules

Subcutaneous nodules are a relatively uncommon finding in ARF, but careful inspection will reveal them in approximately 20% of patients, especially among those with significant cardiac involvement. When present, these painless nodules are most typically found overlying the bony prominences of the elbows and ankles.

## 12.5 Establishing a Diagnosis of Acute Rheumatic Fever

As noted, combinations of major and/or minor diagnostic criteria and definitive evidence of an antecedent group A streptococcal infection are necessary to establish a diagnosis

**Call Out Box 12.3**
The Jones criteria have been used to diagnose acute rheumatic fever for several decades. Acute carditis and long-term cardiac sequelae in the form of rheumatic heart disease are the most feared complication of the illness. The 2015 update of the Jones criteria includes changes in both the major and minor diagnostic criteria from prior iterations.

of ARF. Laboratory testing is important to aid in the determination that a recent group A streptococcal infection was likely. Serologic testing for the presence of antistreptococcal antibodies should include two or more of the following: antistreptolysin O (ASO), anti-deoxyribonuclease B, anti-hyaluronidase, anti-streptokinase, and anti-nicotinamide-adenine-dinucleotidase. Serial testing that demonstrate clear patterns of rising antibody levels are considered more specific than antibody titers measured at a single point in time. Of the antibodies listed, the ASO titer is most commonly used. In children, ASO titers of 333 Todd units or higher are considered positive. Cultures and antigen detection tests for group A streptococcus can also be performed on material collected by swabbing the pharynx, but most patients already have negative results by the time symptoms of ARF appear. Echocardiography has become central for the diagnosis of carditis, superseding the prior reliance on chest auscultation for the presence of new heart murmurs. The 2015 ARF guidelines recommend echocardiograms with Doppler in all patients with suspected or confirmed ARF [8, 15, 23] [► Call Out Box 12.3].

## 12.6 Treatment of Acute Rheumatic Fever

### 12.6.1 Antibiotics

Most patients who are diagnosed with ARF will have negative throat cultures for group A streptococcus. Despite this observation, the antecedent *Streptococcus pyogenes* infection should always be treated with antibiotics. The drug of choice is oral penicillin for a total duration of 10 days. Amoxicillin and intramuscular penicillin G can also be used. Alternative antibiotics for those who are allergic to or intolerant of penicillin include oral cephalosporins and macrolides. To date, group A streptococcus isolates have been universally susceptible to all β-lactam antibiotics including all penicillins and all cephalosporins. Macrolides class antibiotics should only be used if the patient has a true type-1 hypersensitivity to penicillin because a small percentage of *S. pyogenes* isolates are macrolide-resistant. When using a macrolide class antibiotic to treat a moderate to severe, culture positive *S. pyogenes* infection, it is important to request that the microbiology laboratory perform antibiotic susceptibility testing on the isolate to be sure the organism is macrolide susceptible.

Another key component of the management of ARF is the initiation of secondary prophylaxis. Prophylaxis is given to prevent recurrences of group A streptococcal infection as soon as the initial treatment course has been completed. Monthly intramuscular injections of a long-acting penicillin or daily oral penicillin are both acceptable options. Some patients prefer the discomfort of the monthly injections over the hassle of taking daily medication. Current recommendations support the administration of secondary prophylaxis in patients with ARF with cardiac sequelae until the age of 40 years or for 10 years following their diagnosis, whichever is longer. Individuals diagnosed with ARF who do not have evidence of carditis should continue antibiotic prophylaxis until 21 years of age or for 5 years following their diagnosis, whichever is longer. Individuals diagnosed with ARF with evidence of carditis but without valvular sequelae should continue antibiotic prophylaxis until 21 years of age or for 10 years following their diagnosis, whichever is longer.

### 12.6.2 Other Medications Used in the Treatment of Acute Rheumatic Fever

Neither glucocorticoids nor immune globulin intravenous (IgIV) have proven beneficial in altering the cardiac outcomes when used as adjunctive treatment for ARF [27]. The use of glucocorticoids as adjunctive therapy for Sydenham's chorea, however, does appear beneficial, especially for more severe neurologic manifestations of the disease [28]. Immune globulin intravenous (IgIV) has not proven useful for the treatment of Sydenham's chorea.

Other anti-inflammatory agents such as nonsteroidal anti-inflammatory drugs (NSAIDs) and salicylates do not attenuate the severity of ARF-associated carditis or chorea. These medications are useful, however, for the treatment of fever, arthralgia, and arthritis. Aspirin is considered the most effective agent and is usually administered for the duration of the patient's symptoms [29].

Historically, bed rest was recommended as part of the therapeutic regimen for ARF but is no longer routinely recommended [30] [► Call Out Box 12.4].

A safe and effective vaccine to prevent group A streptococcal infections has remained elusive despite decades of effort. Unlike the growing list of vaccine-preventable infections, bouts of streptococcal pharyngitis, even when quite severe, do

**Call Out Box 12.4**
Appropriate antibiotics (penicillin being the drug of choice) are essential for primary treatment and secondary prevention of acute rheumatic fever. Glucocorticoids are a useful adjunct for the treatment of Sydenham's chorea but have not proven beneficial for carditis.

not result in protection from reinfection. The lack of a true surrogate of protective immunity is a key obstacle to the development of a vaccine. Strain to strain variability in the immunodominant bacterial epitopes are an added challenge [31]. The potential for inciting autoimmune phenomenon with candidate vaccines must also be considered during the development and implementation of any new clinical vaccine trial.

## 12.7 Exercises

Please refer to the supplementary information section for answers to these exercises.

1. You are working in the emergency department at a hospital in Hawaii. A 10-year-old girl presents with complaints of 4 days of fever, joint pains, painless bumps on her elbow, and a rash. Her parents tell you that she was seen at urgent care for a sore throat about 2 weeks ago and diagnosed with viral pharyngitis. That illness was not treated with antibiotics. On physical examination, she has a fever of 38.5 °C; an erythematous, serpiginous rash on her trunk, abdomen, and left arm; and three small painless nodules over the bony prominence of her right elbow. Her heart and lung examination are normal. She complains of discomfort when moving her elbows, knees, and hips, but no obvious redness or swelling of the joints is appreciated. Of the following options, the most likely diagnosis is:
   1. Acute rheumatic fever
   2. Parvovirus infection
   3. Coxsackievirus infection
   4. Systemic lupus erythematosus

2. Glucocorticoids have been shown to be beneficial adjunctive treatment for which of the following manifestations of acute rheumatic fever?
   1. Sydenham's chorea
   2. Pancarditis
   3. A and B
   4. None of the above

3. Which heart valve is most commonly affected by rheumatic carditis?
   1. Mitral
   2. Aortic
   3. Tricuspid
   4. Pulmonary

4. All patients with a diagnosis of rheumatic fever should receive secondary penicillin prophylaxis. True or false?

5. Acute rheumatic fever is a nonsuppurative complication of group A streptococcal pharyngitis, impetigo, cellulitis, pneumonia, and bacteremia. True or false?

## 12.8 Summary

ARF and RHD are associated with significant morbidity and mortality. Even though ARF has largely been eliminated from the continental USA and much of Europe, it remains a significant problem worldwide. The disease has devastating consequences if not diagnosed and managed appropriately, disproportionately affecting individuals of lower socioeconomic class and low- to middle-income countries. The precise mechanisms of pathogenesis of ARF remain unclear, and a safe and effective vaccine has remained elusive. Clinicians need to a good grasp of the diagnostic Jones criteria so that the disease can be recognized and treated early in its course.

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# Infections of the Liver and Intestinal Tract

Contents

# Infectious Hepatitis

## Fever, Abdominal Pain, and Elevated Serum Aminotransferases

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**Learning Objectives**

- Describe the etiologies of infectious hepatitis.
- Distinguish between the clinical features of infectious hepatitis.
- Determine the appropriate diagnostic testing for infectious hepatitis.
- Describe preventive measures available for infectious hepatitis.
- Recognize the various antiviral agents used for the treatment of chronic viral hepatitis infections.

## 13.1 Definitions

*Aminotransferases* – enzymes that transfer amino groups from an amino acid to a keto acid. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST), normally present at low concentrations in the serum, are released by injured hepatocytes. Thus, an increase in serum ALT and AST concentrations may signify acute liver injury.

*Cirrhosis* – end-stage, diffuse, and progressive, hepatic fibrosis.

*Sustained virologic response after treatment for hepatitis C* – undetectable *hepatitis C virus* RNA at least 12 weeks after the completion of antiviral therapy.

## 13.2 Introduction

Infectious hepatitis may be caused by a variety of diverse pathogens [▶ Call Out Box 13.1]. Some of these infecting agents are specifically hepatotropic in nature, such as *hepatitis A virus*, with injury and illness restricted primarily to the liver, while others, such as *Epstein-Barr virus* (EBV), may induce liver injury during systemic illness involving multiple organ systems. This chapter focuses on the infectious disease evaluation of a patient who presents with acute or chronic hepatitis. It is important to recognize that many noninfectious conditions can also cause acute and chronic liver inflammation.

**Call Out Box 13.1**

**Infectious Etiologies of Hepatitis**

| Hepatotropic viruses | Systemic viral illnesses associated with hepatitis |
|---|---|
| *Hepatitis A virus* | *Epstein-Barr virus* |
| *Hepatitis B virus* | *Cytomegalovirus* |
| *Hepatitis C virus* | *Arboviruses (dengue, yellow fever)* |
| *Hepatitis D virus* | *Varicella-zoster virus* |
| *Hepatitis E virus* | *Human immunodeficiency virus* |
| | Hemorrhagic fever viruses |
| | *Parvovirus B-19* |

**Systemic Viral Illnesses Associated with Severe Neonatal Hepatitis**

- *Herpes simplex viruses*
- *Enteroviruses*
- *Adenoviruses*

**Organisms Associated with Liver Abscess**

- *Staphylococcus aureus*
- *Bacteroides fragilis*
- *Fusobacterium necrophorum*
- *Entamoeba histolytica*

## 13.3 Clinical Evaluation

Infectious hepatitis may be acute or chronic, with clinical manifestations that span the spectrum from asymptomatic disease to fulminant hepatitis with liver necrosis. The evaluation of patients found to have elevated liver enzymes should begin with a detailed history and physical examination. The patient's age, underlying medical history, and family history of liver disease may reveal conditions that predispose the patient to hepatitis. Exposure to hepatotoxic medications, including but not limited to acetaminophen, valproic acid, or isoniazid, accounts for approximately 10% of all acute cases of hepatitis [1]. Furthermore, while many herbal supplements are found to have liver-protecting effects, there are products which result in significant liver damage, such as Shou-Wu Pian (*Polygonum multiflorum*), a Chinese supplement used to stimulate hair growth, and Kava (*Piper methysticum*), an herbal supplement used to treat anxiety [1]. A recent case series reported by the US Centers for Disease Control and Prevention also described acute liver failure from ingestion of *Amanita phalloides*, a species of wild mushroom known to contain amatoxin, a hepatocyte poison [2]. Thus, obtaining the detailed medical history should include asking about exposure to over-the-counter products, prescription medications, and any ingested herbal or natural products.

Risk factors should also be assessed during the medical history, including travel, chronic illness associated with a compromised immune system, use of alcohol or intravenous drugs, and sexual practices [▶ Call Out Box 13.2]. Alcoholic hepatitis, a life-threatening complication seen with chronic alcohol consumption, is a diagnosis of exclusion dependent on obtaining a thorough history of alcohol use [3]. Intravenous drug use (IVDU) can cause hepatic injury directly or can place the patient at risk for acquiring hepatitis B (HBV) and hepatitis C (HCV) viruses if they share drug paraphernalia with an infected individual. Other patient populations at risk for acquiring hepatitis B or C include infants born to mothers infected with the virus, people who received blood transfusions or solid organ transplants before 1992, sexual partners of those infected with the virus, men who have sex with men, and chronic hemodialysis.

Clinically, the presence of an acute febrile syndrome with vomiting, anorexia, abdominal pain, fatigue, weight loss, and jaundice is consistent with acute infectious hepatitis. Patients with chronic hepatitis are typically asymptomatic until complications of chronic liver disease occur later in life. In the absence of known or recognized risk factors, many chronic hepatitis B and C infections are diagnosed

**Call Out Box 13.2**

**Infectious hepatitis etiologies by risk factors**

| Men who have sex with men | Severely immunocompromised | Travel | Intravenous drug users (IVDU) | Chronic granulomatous disease |
|---|---|---|---|---|
| *Hepatitis A virus* | *Epstein-Barr virus* | *Hepatitis A virus* | *Hepatitis B virus* | *Staphylococcus aureus* liver abscess |
| *Hepatitis B virus* | *Cytomegalovirus* | *Hepatitis E virus* | *Hepatitis C virus* | |
| *Hepatitis C virus* | *Herpes simplex virus* | *Entamoeba histolytica* | *Human immunodeficiency virus* | |
| *Human immunodeficiency virus* | *Varicella-zoster virus* | *Arboviruses* Hemorrhagic fever viruses | | |
| | *Histoplasma capsulatum* | | | |

after elevated serum aminotransaminases are often discovered on routine screening or during an evaluation for another illness. While the elevation of these serum enzymes is nonspecific, the observation triggers the provider to include specific testing for these infections during the diagnostic evaluation.

The key physical examination findings in a patient with acute infectious hepatitis include scleral, mucosal, or cutaneous icterus, hepatosplenomegaly, tenderness to palpation of the right upper quadrant of the abdomen, presence of ascites or edema, and/or spider angiomas of the skin. While the focus of the physical examination is on the abdomen, a thorough evaluation of all other organ systems should be done to determine the presence or absence of extrahepatic manifestations. In the acute setting, a constellation of signs and symptoms that includes fevers, exudative pharyngitis, lymphadenopathy, and/or generalized rash is suggestive of *Adenovirus* infection, EBV infection, or acute retroviral syndrome caused by infection with *human immunodeficiency virus* (HIV) [4–7]. The presence of a febrile respiratory illness with a vesicular rash could indicate an infection with *Varicella-zoster virus* (VZV, "chickenpox"). The finding of arthritis on physical examination in a patient with hepatitis can be seen with both HBV and HCV infection [8, 9]. Lichen planus, a cell-mediated immune response that includes pruritic lesions on the flexural surface of the extremities, is associated with HCV infection, while Gianotti-Crosti syndrome, a lenticular, flat, erythematous rash, resulting from circulating immune complexes, can be manifestations of HBV or EBV infection [8–11]. Similarly, a "serum sickness-like" reaction, characterized by fevers, rash, and arthritis, has been seen in some patients with HBV infection [9].

Neonates with hepatitis secondary to an acute viral infection can present with viral sepsis. Symptoms include temperature instability which may manifest as fevers or hypothermia, respiratory distress, hepatic failure, and disseminated intravascular coagulation [12–14]. Liver transplantation can be lifesaving, but newborns with such advanced disease typically die before transplantation can be arranged. *Herpes simplex viruses* (HSV), *Enteroviruses*, and *Adenoviruses* each have the potential to cause such life-threatening infections in this age group.

## 13.4 Diagnostic Evaluation of a Patient with Hepatitis

Hepatitis is reflected by a significant elevation of the liver enzymes, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) . Evidence that the hepatocellular damage is leading to cholestasis is reflected in increases in serum concentrations of conjugated bilirubin, alkaline phosphatase, and γ-glutamyl transpeptidase. It is important to note that while ALT is more specific to hepatocyte damage than AST, both enzymes are also produced and released by other cell types including cardiac and skeletal myocytes.

The general evaluation of a patient with elevated serum transaminase levels should include a complete blood count with differential, complete metabolic panel, hepatic function tests, which include serum albumin, blood prothrombin time (PT), and a calculated international normalized ratio (INR). These results, in combination with a complete history and physical examination, help to determine the severity of liver disease and provide guidance for other diagnostic tests that should be considered. For example, the presence of circulating atypical lymphocytes could indicate EBV infection as the underlying cause of the hepatitis. Of note, while the absolute degree of the transaminase elevation does not always correlate with the severity of the liver injury, a patient who is found to have decreasing transaminase concentrations together with a decrease in serum albumin and increasing serum bilirubin, PT, and INR may signify irreversible fulminant hepatitis with liver necrosis.

Abdominal imaging using ultrasonography, computed tomography (CT), or magnetic resonance imaging (MRI) may be helpful during the diagnostic evaluation. Hepatic granulomas, seen on imaging or during histopathologic analysis of biopsied tissue, have been described with

disseminated *Bartonella henselae* infection [15–17]. Similarly, imaging can help identify liver abscesses due to bacterial or parasitic infection. Imaging may also provide evidence to support the presence of hepatic fibrosis, cirrhosis, or hepatocellular carcinoma (HCC).

Diagnostic testing to identify the specific etiology of infectious hepatitis should also be pursued. Hepatitis A, B, C, D, and E and infections with EBV, CMV, HIV, VZV, or *B. henselae* can all be diagnosed serologically. Other viral agents, such as HSV, *Enteroviruses*, and *Adenoviruses*, are best identified using polymerase chain reaction (PCR) testing for virus detection from liver biopsy material, whole blood, nasopharyngeal secretions, cerebrospinal fluid, or other body fluids.

## 13.5 Infectious Causes of Hepatitis

### 13.5.1 Commonly Encountered Hepatotropic Viruses

#### 13.5.1.1 Hepatitis A Virus (HAV) Infection

HAV is the most prevalent hepatotropic virus (◘ Table 13.1). Human to human transmission occurs via the fecal-oral route, most commonly through direct contact with an infected person. The virus gains entry to the liver through the gastrointestinal tract, reaching the liver through the portal venous system. Virus replication occurs in the hepatocytes, causing direct cytolytic and immune-mediated liver injury. Newly produced virus is then released through the bile, into the intestines, and excreted in the stool [18]. Young children tend to be minimally symptomatic with infection, and since they almost never develop icterus, the diagnosis of infectious hepatitis is not considered until an adult contact, such as a parent or teacher, develops symptomatic disease with classic signs and symptoms [► Call Out Box 13.3]. As such, children act as a major source of transmission of HAV to both household contacts as well as the community through schools, day cares, and recreational camps [18].

HAV infection occurs throughout the world, mainly in areas with poor living conditions such as overcrowding, poor sanitation infrastructure, and poor personal hygiene [19]. The primary risk factors for acquiring HAV infection include the ingestion of contaminated food and water, travel to

**Call Out Box 13.3**
Young children who are infected with hepatitis A are typically only minimally symptomatic if symptomatic at all. They don't develop the classic feature of icterus, so a diagnosis of infectious hepatitis is not considered until an older, close contact develops more classic signs and symptoms of disease. As such, when the index case is a young child, it is not unusual for multiple exposures to occur, resulting in sizable community-wide outbreaks of disease.

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◘ **Table 13.1** Comparisons between the five hepatotropic viruses

| | Hepatitis A | Hepatitis B | Hepatitis C | Hepatitis D | Hepatitis E |
|---|---|---|---|---|---|
| Modes of transmission | Fecal-oral | Vertical<br>Transfusion<br>IV drug use<br>Sexual activity | Vertical<br>Transfusion<br>IV drug use<br>Sexual activity | Vertical<br>Transfusion<br>IV drug use<br>Sexual activity | Fecal-oral |
| Clinical features | Jaundice<br>Nausea<br>Diarrhea<br>Abdominal pain<br>Anorexia<br>Fatigue<br>Fever | Jaundice<br>Nausea<br>Diarrhea<br>Abdominal pain<br>Anorexia<br>Fatigue<br>Fever<br>Pruritic rash | Jaundice<br>Nausea<br>Diarrhea<br>Abdominal pain<br>Anorexia<br>Fatigue<br>Fever<br>Pruritic rash | Jaundice<br>Nausea<br>Diarrhea<br>Abdominal pain<br>Anorexia<br>Fatigue<br>Fever<br>Pruritic rash | Jaundice<br>Nausea<br>Diarrhea<br>Abdominal pain<br>Anorexia<br>Fatigue<br>Fever |
| Diagnostic testing | Serology (HAV IgM/IgG) | Serology (HBsAg, HBsAb,HBcAb IgM)<br>PCR | Serology (HCV IgG)<br>PCR | Serology (HDV IgM) | Serology (HEV IgM) |
| Treatment | Supportive care | Supportive care<br>Antiviral therapy for selective patients | Supportive care<br>Antiviral therapy for most patients | Supportive care<br>Antiviral therapy for selective patients | Supportive care |
| Chronic infection | No | Yes | Yes | Yes | No |
| Prevention | Vaccination<br>Pooled immunoglobulin | Screening<br>HBIG<br>Vaccination | Screening | None | Vaccination (only available in China) |

endemic areas, illicit drug use, men who have sex with men, and exposure to daycare centers [20–23].

The incubation period for HAV is approximately 30 days with a range of 15–50 days. While most young children infected with HAV are minimally symptomatic, the classic clinical picture among older children and adults includes fever, abdominal pain, jaundice, nausea, decreased appetite, and prolonged fatigue. Complications from hepatitis A infection are extremely rare but do include fulminant hepatitis, pancreatitis, autoimmune hemolytic anemia, acute kidney injury, and arthritis. Relapsing hepatitis, for periods as long as 6 months after primary infection, has also been described.

The diagnosis of acute HAV infection is confirmed by the presence of immunoglobulin M directed against HAV (anti-HAV IgM). The IgM response develops within 4 weeks of symptom onset. Anti-HAV IgG antibody can be detected within 8 weeks of symptom onset and confers long-term protection. The presence of anti-HAV IgG in the absence of anti-HAV IgM indicates either past infection or prior immunization against the disease. During HAV infection, serum aminotransaminases are expected to peak at the onset of jaundice and rapidly return to the normal range over the next 2–3 weeks. In some cases, the transaminase elevation can persist for several months.

The management of acute HAV infection involves supportive care, including intravenous hydration, if needed. No specific treatments are available. Infection can be prevented through the use of either passive or active immunization. The Advisory Committee on Immunization Practices (ACIP) recommends that all children receive the 2-dose series of hepatitis A vaccine beginning at 12 months of age. Other populations who should receive the hepatitis A vaccine series include travelers to or working in countries that have high or intermediate endemicity of infection, men who have sex with men, illicit drug users, and patients with chronic liver disease. Passive immunization is achieved through the use of pooled human immunoglobulin. The product can be administered to unvaccinated people who have been exposed to HAV in the previous 2 weeks and to those who are traveling to an HAV-endemic area and are unable to be immunized [23].

#### 13.5.1.2 Hepatitis B Virus (HBV) Infection

HBV, a leading cause of cirrhosis and hepatocellular carcinoma (HCC), is an oncogenic, enveloped circular DNA virus (◘ Table 13.1). The HBV virion consists of a core containing the viral genome, reverse transcriptase, and the HBV e-antigen (HBeAg) surrounded by an inner nucleocapsid containing the HBV core antigen (HBcAg). The core and inner nucleocapsid are surrounded by an envelope containing the HBV surface antigen (HBsAg) [ 24]. Unlike other hepatotropic viruses, the liver injury from HBV infection is due primarily to the immune response to infection, not as a result of direct viral cytotoxicity.

The primary mode of transmission of infection varies by geographic location. In areas of high HBV endemicity, such as sub-Saharan Africa, Latin America, Central Europe, and Southeast Asia, infection occurs most commonly through vertical transmission from mother to child. The risk of perinatally acquired infection among hepatitis B-infected, HBeAg-positive infected mothers exceeds 65% [25]. In developed countries, where HBV is not endemic, infection is more commonly transmitted following exposure to infected blood or body fluids [26].

The incubation period for HBV is 28–180 days (mean 80 days). HBV infection in infants and young children tends to be asymptomatic, whereas older children and adults may present with symptoms typically associated with acute hepatitis including fever, nausea, malaise, abdominal pain, and jaundice. Extraintestinal manifestations may present before the actual onset of jaundice, including migratory polyarthritis, urticarial or maculopapular rash (including Gianotti-Crosti syndrome), and glomerulonephritis. Any patient diagnosed with HBV infection who presents with fulminant hepatitis or acute liver failure should be evaluated for coinfection with HDV. Fifteen to forty percent of individuals with untreated chronic HBV infection ultimately develop complications such as cirrhosis, liver failure, and HCC. HCC is the third leading cause of neoplastic-related mortality in the world, and the majority of cases are related to chronic HBV infection [27]. The risk factors for the development of HCC include chronic HBV infection, male gender, cirrhosis, and a family history of HBV-associated HCC.

The interpretation of diagnostic serologic markers in HBV infection is fairly straightforward but requires consideration of several different laboratory results in combination. The laboratory will provide results for the detection of hepatitis B surface antigen (HBsAg), IgG antibody directed against it (HBsAb), hepatitis B e-antigen (HBeAg) and IgG antibody directed against it (HBeAb), and IgM antibody directed against hepatitis B core antigen (HBcAb). HBV-DNA quantification provides information about the patient's viral load (◘ Fig. 13.1).

In almost every circumstance, the detection of serum HBsAg indicates that the patient is infected with HBV [▶ Call Out Box 13.4]. The detection of HBcAb indicates acute HBV infection. In circumstances where acute infection is cleared by the patient's immune system, HBsAg disappears over a period of weeks to months. During the same time period, HBcAb becomes detectable. The time between the loss of HBsAg and the development of HBV antibodies is termed the "window period" of infection because laboratory results incorrectly appear to indicate the absence of infection.

The presence of HBeAg indicates high rates of virus replication. Individuals with hepatitis B e-antigenemia are highly contagious. The ability to detect HBsAg for more than a 6-month period defines chronic HBV infection. Chronic HBV infection can be divided further into two main phases, which is important because the phase of infection helps guide therapeutic decision-making. The immune-tolerant phase is characterized by a very high viral load, the presence of HBeAg, and minimal evidence of liver inflammation or injury. The serum transaminase concentrations are often found to be in the normal range. The immune-tolerant phase is followed by an immune-active phase which is also characterized by high viral load, but serum transaminases are elevated. Serum HBeAg may persist, but this is the phase

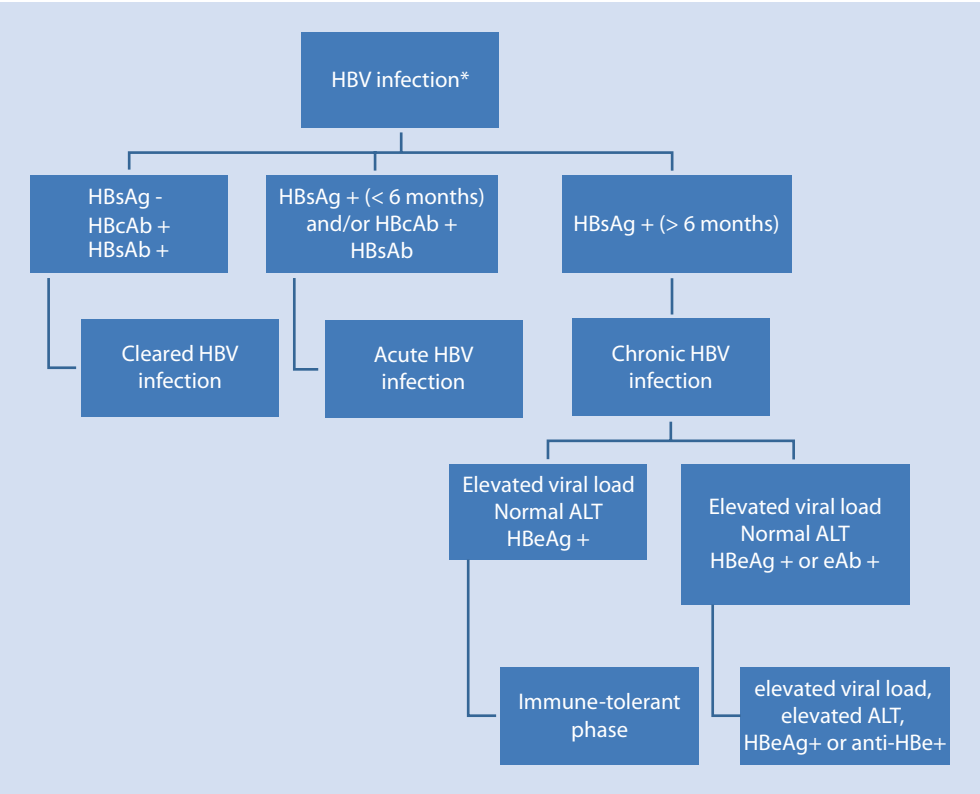


**Fig. 13.1** The interpretation of diagnostic serologic markers in HBV infection is fairly straightforward but requires consideration of several different laboratory results in combination. HBV *Hepatitis B virus*, HBsAg HBV surface antigen, HBsAb HBV surface antibody, HBcAb HBV core antibody, HBeAg HBV e-antigen, ALT alanine aminotransferase. Of note, the presence of HBV surface antibody with a negative HBV core antibody indicates past immunization, not infection

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**Call Out Box 13.4**

The detection of serum hepatitis B surface antigen (HBsAg) indicates that the viral antigen is circulating in the patient's bloodstream. When performed on a patient with acute hepatitis, the logical interpretation is that the cause of the patient's illness is acute hepatitis B. Surface antigen is also present during chronic infection because *hepatitis B virus* continues to circulate, and the assay used to detect surface antigen is quite sensitive. It's also important to remember that the current hepatitis B vaccine is comprised of highly purified, recombinant hepatitis B surface antigen because the antigen can be detected in the blood for several days after immunization. This marks a circumstance where the surface antigen is present, but its presence does not indicate a hepatitis B infection.

where individuals develop HBeAb [28, 29]. Typically, children with perinatally acquired HBV infection remain in an immune-tolerant state until puberty, at which time some will convert to the immune-active phase with development of antibody directed against the hepatitis e-antigen.

The accepted surrogate of immunity to HBV is the presence of HBsAb at concentrations of 10 mIU/ml or higher. It is important to remember that the presence of both HBsAb and HBcAb indicate a past, resolved HBV infection. In contrast, the presence of HBsAb in the absence of HBcAb indicates protection against HBV infection as a result of having been immunized.

Any patient with chronic HBV infection who developed rapid progression to severe liver disease should be evaluated for HDV superinfection. This is achieved through serologic testing to detect the presence of anti-HDV antibodies (Table 13.1).

The goals of treatment for chronic HBV infection are to clear HBV-DNA from the bloodstream, to normalize the ALT level, and to achieve seroconversion against the hepatitis B e-antigen. The use of antiviral medications is specifically recommended for chronic hepatitis B infections in the immune-active phase (high viral load with elevated serum transaminases) for 6 months or longer without the development of HBeAb. Currently, there are six therapeutic agents approved in the United States for the treatment of patients with chronic HBV infection: pegylated-interferon alpha, lamivudine, telbivudine, entecavir, tenofovir, and adefovir [29]. Traditional HBV therapy included the use of interferon alpha, but its use has fallen from favor largely because of the frequency and severity of the medication-associated fevers, myalgias, and fatigue. Other adverse reactions associated with the use of interferon alpha included the development of autoimmune, ischemic, and neuropsychiatric problems [29].

All patients diagnosed with chronic HBV infection should be screened for coinfection with *human immunodeficiency virus* (HIV) and HCV because the presence of coinfection(s) changes the preferred therapeutic antiviral regimens.

Patients with chronic HBV infection should be counseled on ways to avoid further liver insult, such as avoiding hepatotoxic medications, avoiding alcohol consumption, and making sure that they are fully immunized against HAV. At a minimum, annual screening for the development of HCC should be performed by undergoing liver ultrasonography and a serum alpha-fetoprotein (AFP) measurement.

Prevention of HBV infection can be achieved through the use of either passive or active immunization. Passive immunization, through the use of hepatitis B immunoglobulin (HBIG), a pooled plasma product consisting of high titers of HBsAb, provides immediate protection after recent exposure among unimmunized individuals. It is best used in combination with active vaccination for infants born to HBV-infected mothers and occupational, or sexual contact, exposures to HBV. The protection provided by HBIG is short-lived, lasting only 3–6 months from the time of administration. Long-term protection from HBV infection, however, is provided by active immunization with the hepatitis B vaccine [26, 30].

Current HBV prevention recommendations include (1) testing all pregnant women for HBsAg, (2) immunizing all babies born to mothers with positive HBsAg with HBIG and HBV vaccine within 12 h of birth followed by timely completion of the HBV vaccine series, (3) immunizing all babies born to mothers whose HBsAg is unknown with HBV vaccine and immediately checking maternal HBsAg to determine if the baby should receive HBIG, followed by timely completion of the HBV vaccine series, and (4) universal immunization of all babies born to HBsAg negative mothers with the complete HBV vaccine series. In addition, all unvaccinated children and adolescents <19 years of age should complete the HBV vaccination series [26]. In adults, HBV vaccination is recommended for those with a HBsAg-positive sexual partner, those with multiple sexual partners, those seeking evaluation or treatment for a sexually transmitted diseases, those who are traveling to a high or intermediate endemic area, those who have chronic liver disease, those who are HIV-infected, and those who are at risk for infection by percutaneous or mucosal exposure to infected blood, including individuals with a current or past history of IVDU and household contacts of HBV-infected patients, healthcare workers, emergency responders, and chronic dialysis patients [30].

### 13.5.1.3 Hepatitis C Virus (HCV) Infection

HCV is an oncogenic, enveloped, single-stranded, positive sense RNA virus with six major genotypes. Substantial variation exists among genotypes with regard to geographic distribution, clinical course of the infection, and response to therapy (◘ Table 13.1).

In the United States, chronic HCV infection is a leading indication for liver transplantation. Intravenous drug use and receipt of a blood transfusion product before 1992 are major risk factors for chronic infection [31]. Additional risk factors for acquiring HCV infection include multiple sexual partners, a requirement for hemodialysis, and percutaneous exposure through occupational risk, tattoos, or piercings. Perinatal transmission of HCV infection from mother to child occurs at a rate of approximately 5%, but may be higher among women with very high HCV viral loads at the time of delivery and among those who are coinfected with HIV [32, 33]. Eighty percent of individuals who acquire HCV infection will develop chronic liver disease if left untreated [33].

**Call Out Box 13.5**
Cryoglobulinemia refers to the presence of circulating immunoglobulins that become insoluble at reduced temperatures. Suspect this condition when you observe injury, necrosis, or infarction in the distal extremities, and in patients with unexplained vasculitis. Cryoglobulinemia is a very unusual condition. Any patient discovered with this condition should have testing for HCV infection included in their diagnostic evaluation.

The incubation period for HCV infection is 4–8 weeks. HCV infection of the infant and young child is typically asymptomatic. Older children and adults may present with symptoms typical of other causes of acute infectious hepatitis including jaundice, malaise, abdominal pain, and anorexia. Extrahepatic manifestations of HCV infection include vasculitis, membranoproliferative glomerulonephritis, insulin resistance, neuropathy, and cryoglobulinemia [▶ Call Out Box 13.5] [32, 33]. Although most children with chronic HCV infection are asymptomatic during their early years, the vast majority will develop chronic hepatitis with fibrosis beginning in their adolescent and young adult years. Fulminant hepatitis with acute liver failure is rare with HCV infection; however, approximately one-fifth of all infected patients will ultimately develop end-stage liver disease if not treated [34].

Two types of diagnostic tests are available for HCV infection. Nucleic acid amplification testing (NAAT) detects the presence of HCV RNA in the blood, while antibody testing determines whether the patient has been infected with the virus. For screening purposes, antibody testing is preferred because it is less expensive and has a faster turnaround time. The detection of anti-HCV IgG antibody, however, does not allow a determination about the current infection status since the antibody is present whether the patient previously cleared the infection or continues to have a chronic infection. Infants born to HCV-infected mothers should be evaluated using the NAAT test, as the presence and detection of passively acquired maternal HCV Ab can persist for up to 18 months and reveals nothing about the infant's HCV infection status.

All patients with positive HCV antibody screening tests should undergo NAAT. Once the diagnosis of ongoing HCV infection has been confirmed with a NAAT, results of virus genotyping guide the optimal medical management.

The ultimate goal of HCV therapy is to reduce HCV-associated liver disease, including cirrhosis and hepatocellular carcinoma. Currently available antiviral treatment regimens are highly effective at achieving a sustained virologic response (SVR), the term used to indicate that the chronic infection is cured. Antiviral treatment is therefore recommended for all individuals with chronic HCV infection who do not have an otherwise shortened life expectancy [35].

Historically, combination antiviral therapy with interferon alpha and ribavirin yielded a suboptimal sustained virologic response and was associated with significant

adverse effects, including influenza-like symptoms, leukopenia, and anemia. More recently, the development of direct-acting antiviral therapy for the treatment of HCV infection has been associated with impressive SVR with fewer adverse effects. These antiviral agents target nonstructural (NS) viral proteins that are essential for viral replication including the NS3 and NS4A viral proteases, the NS5B RNA-dependent RNA polymerase, and the NS5A phosphoprotein. SVR achievement is associated with a 70% risk reduction in the development of HCC and a 90% risk reduction in development of liver-related deaths and transplantation needs [35]. While the newer antiviral agents do pose a significant financial burden on the healthcare system, early treatment of HCV infection may reduce future costs of complications from chronic liver disease.

All patients diagnosed with chronic HCV infection should be screened for coinfection with *human immunodeficiency virus* (HIV) and HBV since the optimal antiviral regimen may differ when patients need treatment for more than one viral infection. Furthermore, all HCV-infected patients should be immunized against HAV and HBV. Yearly screening for HCC with liver ultrasonography and measurements of serum alpha-fetoprotein (AFP), a highly sensitive HCC tumor marker, is also recommended.

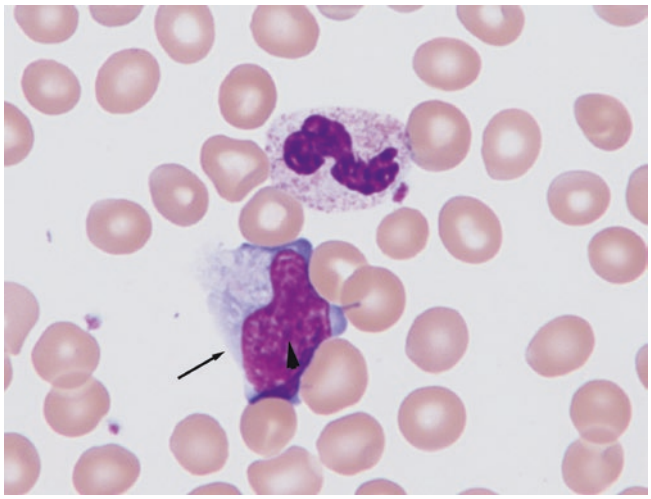

**Fig. 13.2** Shown is a peripheral blood smear from a patient with *Epstein-Barr virus* associated with infectious mononucleosis. The lymphocyte (arrow) seen here is "atypical" because it contains a large amount of cytoplasm and has demonstrable nucleoli easily visible in its nucleus (arrowhead). The cytoplasm of atypical lymphocytes often appears to be indented by surrounding erythrocytes. During the acute phase of infectious mononucleosis, it is not unusual for atypical lymphocytes to account for 30% or more of the circulating leukocytes. Photomicrograph is kindly provided by Dr. Scott Riddell

### 13.5.2 Hepatotrophic Viruses That Cause Systemic Illness

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Many acute viral infections are associated with some degree of liver involvement. In this section, systemic viral infections that typically cause moderate to severe hepatitis are discussed. In many of these cases, the final clue that implicates the underlying viral etiology of the patient's illness is the unexpected finding of elevated serum hepatic transaminases during the review of the patient's initial laboratory test results.

#### 13.5.2.1 Epstein-Barr Virus (EBV) Infection

More than 90% of adults have serologic evidence of past EBV infection [36]. The primary mode of transmission is through exposure to infected saliva explaining how the classic illness of infectious mononucleosis earned its nickname, "the kissing disease." Despite the nickname, the vast majority of infections are transmitted from person-to-person through the behavior of sharing eating and drinking utensils. Less common modes of transmission include spread via sexual contact, or through receipt of blood products or transplantation [36].

The incubation period for EBV can be as long as 8 weeks. Many cases are asymptomatic. When symptomatic, adolescents and young adults most typically develop the syndrome referred to as infectious mononucleosis, a collection of signs and symptoms that include exudative pharyngitis, generalized lymphadenopathy, splenomegaly, and atypical lymphocytosis on the peripheral blood smear (Fig. 13.2). The vast majority of patients with acute EBV infection will demonstrate an elevation in serum hepatic transaminases, but only about 5% develop hyperbilirubinemia with associated jaundice [37]. Unlike the hepatotropic viruses, EBV infection is associated with minimal hepatocellular damage. The infection is self-limited and has an excellent prognosis [37]. It is important to note that rare underlying conditions are associated with a life-threatening pathologic response to EBV infection. These conditions are associated with EBV-induced lymphoproliferative disorder, hemophagocytic lymphohistiocytosis, autoimmune diseases, and malignancies [38]. Such rare underlying conditions should be considered in patients with severe, progressive, or persistent EBV-associated hepatitis.

The diagnosis of acute EBV infection is based on the results of serologic testing (Table 13.2). The presence of IgM directed against the viral capsid antigen (VCA) is indicative of acute or recent infection. The presence of antibody directed against Epstein-Barr nuclear antigen in combination with a positive VCA IgM suggests recent infection over acute infection because the EBNA IgG antibody takes several weeks or months to be produced. The presence of both VCA IgG and IgG directed against EBNA reflect a past EBV infection.

Another laboratory study that is often requested when acute EBV infection is being considered is the heterophile antibody test. This rapid, often point of care test for possible EBV infection, lacks sensitivity in young children and suffers from a lack of specificity under all circumstances because the antibodies being detected are specifically directed against EBV. Heterophile antibodies can also be detected in the blood from patients with *human immunodeficiency virus* infection, certain malignancies, and autoimmune disorders such as systemic lupus erythematosus.

**Table 13.2** Interpretation of *Epstein-Barr virus* serologic results based on the pattern of the patient's antibody responses

| Viral capsid antigen IgM | Viral capsid antigen IgG | Epstein-Barr nuclear antigen IgG | Epstein-Barr early antigen IgG | Interpretation |
|---|---|---|---|---|
| Not detected | Not detected | Not detected | Not detected | Never infected |
| + | Not detected | Not detected | Not detected | Acute infection |
| + | + | Not detected | Not detected | |
| + | + | + | + | Recent infection |
| + | + | + | Not detected | |
| + | + | Not detected | Not detected | |
| Not detected | + | Not detected | Not detected | |
| Not detected | + | + | Not detected | |
| Not detected | + | + | + | |
| Not detected | + | + | + | Past infection |
| Not detected | + | Not detected | + | |

Since immunocompromised patients may not mount specific antibody responses to any invading pathogen including EBV, the diagnosis of EBV infection can be made by polymerase chain reaction (PCR) testing to detect EBV-specific DNA in serum, plasma, or tissue. Under these circumstances, quantitative PCR is preferred to assist in distinguishing the presence of latent virus from active virus replication.

The treatment for EBV infection is supportive. Patients diagnosed with acute EBV infection should avoid contact sports for 6 weeks from the time of symptom onset to reduce their risk of traumatic splenic rupture. Some providers allow adolescents to return to usual activity earlier than 6 weeks if their spleen is no longer palpable below the left costal margin and their fevers and fatigue have resolved.

#### 13.5.2.2 Cytomegalovirus (CMV) Infection

CMV infection presents in several different ways based primarily on the age and immune status of the host. Infection is self-limited among otherwise healthy children, adolescents, and adults who may develop an infectious mononucleosis syndrome that is clinically indistinguishable from acute EBV infection [39], including the presence of elevated serum transaminases.

The diagnosis of acute CMV infection is made by detecting the presence of CMV IgM antibody. Among immunocompromised patients who may not be capable of mounting a specific antibody response, quantitative PCR testing can be done to detect CMV DNA from blood, tissue, or cerebrospinal fluid samples. Quantitative antigen testing and viral cultures performed on biologic fluids are also available for use in this patient population.

The management of CMV infection in the immunocompetent patient is supportive, and any liver involvement is typically minor. Antiviral treatment options for immunocompromised patients with CMV infection involving one or more organ system include intravenous ganciclovir or oral valganciclovir [39]. CMV-associated hepatitis causes significant morbidity among the immunocompromised population.

### 13.5.3 Special Populations

#### 13.5.3.1 Hepatitis in the Newborn

Neonates who present with hepatitis should be evaluated for an infectious etiology, especially if there are associated symptoms of temperature instability, respiratory distress, or sepsis. Elevated liver enzymes due to a neonatal bacterial infection are typically associated with sepsis secondary to *Streptococcus agalactiae* (group B streptococcus), *Escherichia coli* and other Gram-negative rods, and *Listeria monocytogenes*. Viral sepsis also occurs in neonates, particularly during infections with HSV, *Enteroviruses*, and *Adenoviruses*. Newborns found to have hepatitis should undergo a thorough diagnostic evaluation that includes studies to evaluate for infections and noninfectious causes. The minimal laboratory evaluation for infection includes blood, urine, and cerebrospinal fluid cultures for bacteria and viruses, a complete blood count with differential, electrolytes, creatinine, hepatic transaminases, and a urinalysis. Cerebrospinal fluid should also be sent to biochemical analysis to measure the glucose, total protein concentrations, and cell count and differential. HSV, *Enterovirus*, and *Adenovirus* PCR testing should also be requested from cerebrospinal fluid and blood. In patients with respiratory symptoms, a chest radiograph should be obtained. A nasopharyngeal sample for PCR for respiratory virus detection may identify an *Enterovirus* or *Adenovirus* as the infecting etiology. Surface swabs of conjunctiva, oropharynx, umbilical stump, rectum, and any vesicular skin lesions should be sent for HSV DNA PCR. Empiric therapy with broad-spectrum intravenous antibiotics and acyclovir should be started immediately while awaiting the results of the diagnostic tests.

#### 13.5.3.2 Hepatitis in the Traveler

The diagnostic evaluation for infectious hepatitis in a person who has been traveling should always begin with testing for the usual culprits while also considering potential infectious

causes endemic to the geographic area(s) where the patient has visited. Details regarding the clinical complaints will also typically offer important clues about the underlying cause of the illness.

## Travel Case Example 1

A 30-year-old man presents with fevers, bloody diarrhea, and right upper quadrant pain after traveling to Southeast Asia on vacation. Results of his initial laboratory tests indicate that he has modestly elevated liver transaminases. While a differential diagnosis explaining this constellation of features can certainly be developed, the man's travel history, symptoms, and laboratory findings all strongly suggest infection with the protozoan parasite *Entamoeba histolytica*. The fevers and bloody diarrhea are consistent with amoebic dysentery, while the right upper quadrant pain and elevated hepatic transaminases suggest extraintestinal spread to the liver, with the formation of hepatic abscesses. Abdominal ultrasonography is used to characterize the size and number of abscesses present. Stool should be collected to evaluate for the presence of "ova and parasites," where an astute laboratory technician may identify the presence of amebic trophozoites or cysts. A serologic diagnosis can also be made using a commercially available enzyme immunoassays (EIA) to detect antibodies against *E. histolytica*.

The treatment for *E. histolytica* colitis with liver abscess includes metronidazole or tinidazole followed by a course of an intraluminal amebicide such as iodoquinol or paromomycin to eradicate the ameba from the intestinal lumen. Occasionally, percutaneous drainage of the liver abscess is indicated [40]. If hepatic abscess fluid is collected for diagnostic or therapeutic purposes, the fluid should be sent to the microbiology laboratory for microscopic evaluation, bacterial culture, and Gram stain.

## Travel Case Example 2

A 35-year-old woman who recently took a month-long trip to coastal Peru and Ecuador presents with acute hepatitis. She complains of daily fevers, modest right upper quadrant abdominal pain, and vomiting. On physical examination she appeared moderately ill with obvious skin and scleral icterus. Her initial laboratory evaluation showed markedly elevated hepatic transaminases and conjugated bilirubin. Serologic testing ruled out hepatitis A, B, and C. She returns to have repeat hepatic transaminase and liver function testing performed to monitor the trend of her illness. The differential diagnosis for her acute hepatitis is broad, but the basic characteristics of her illness appear to strongly implicate a hepatotropic virus. The hepatotropic virus that has yet to be explored from a diagnostic standpoint, which is also endemic to much of South America, is *hepatitis E virus*.

*Hepatitis E virus* (HEV) is the most common cause of viral hepatitis globally (Table 13.1). Transmission occurs most commonly through the ingestion of contaminated water [41]. The clinical manifestations of HEV infection are similar to, but more severe than, the presentation of acute HAV infection. Infection during pregnancy is a known risk factor for the development of fulminant hepatitis carrying a 30% fatality rate [42]. The diagnosis of HEV infection can be made by detecting the presence of serum anti-HEV antibody or by detecting HEV RNA from the blood or stool using PCR.

Finally, travelers who present with signs and symptoms of severe systemic disease with associated hepatitis, especially those with thrombocytopenia or hemorrhage, require a diagnostic evaluation that includes hemorrhagic fever viruses. The specific geographic location(s) of travel becomes critically important. Consultation with the US Centers for Disease Control and Prevention and/or the World Health Organization may be necessary to determine which infectious agents should be considered for diagnostic testing.

Examples of viruses that have the potential to cause severe systemic disease with an associated hepatitis, which also have fairly well-defined geographic distribution, include *Crimean-Congo hemorrhagic fever virus*, *Ebola* (and related) *viruses*, *Dengue viruses*, and *Yellow fever virus* [43]. Serologic testing and nucleic acid amplification techniques are used to confirm the suspected diagnosis.



**Case Study**

**Practical Example**

A healthy 12-year-old female presents to the pediatric gastroenterology clinic with a history of chronic hepatitis B infection. She is a refugee from Southeast Asia who arrived in the United States last year with her family. At her screening health visit 1 year ago, she was found to be HBsAg positive. She reports that her mother and two siblings also have chronic hepatitis B infection. The patient's laboratory results from 1 week ago indicate that she is HBsAg positive, HBeAg positive, and HBeAb negative. She has a high HBV DNA viral load, and her hepatic transaminases are within the normal range for her age. She has no abdominal pain, vomiting, or blood in the stool. She denies any jaundice, fever, or rashes. Her physical examination is normal. She is growing well and has a good appetite.

The patient has chronic hepatitis B infection, in the immune tolerant phase (Fig. 13.1). She has not developed HBeAb, and her hepatic transaminases are normal. She is not currently a candidate for treatment with antiviral medication. Chronic HBV infection is endemic in Southeast Asia where vertical transmission is common. Patients with chronic hepatitis B infection should undergo laboratory testing every 6–12 months and liver ultrasonography yearly to monitor the status of their infection.

## 13.6 Exercise

Please refer to the supplementary information section for answers to these exercises.

Of the options provided, select the single best response to the following questions:

1. Which statement about hepatitis A infection is true?
   A. It is the leading cause of fulminant hepatitis in children.
   B. It is associated with the development of chronic hepatitis.
   C. Relapsing disease can occur for as long as 6 months after the initial infection.
   D. Treatment for non-fulminant hepatitis A includes lamivudine for 4 weeks.
   E. The disease severity decreases with increasing age.

2. Which of the following patterns of laboratory results indicate that the patient is in the immune-tolerant phase of chronic *Hepatitis B virus* infection?
   A. HBsAg positive, HBeAg positive, HBV DNA PCR high with normal serum aminotransferases
   B. HBsAg positive, HBV DNA negative, anti-HBe positive, with normal serum aminotransferases
   C. HBsAg negative, anti-HBs positive, anti-HBc negative
   D. HBsAg negative, anti-HBs negative, anti-HBe positive
   E. HBsAg positive, HBV DNA PCR high, HBeAg positive, elevated serum aminotransferases

3. The most common route of transmission for new cases of hepatitis C infection in children in United States and Europe is:
   A. Intravenous drug abuse
   B. Male to male sex
   C. Infected blood products
   D. Vertical transmission
   E. Contaminated water or food

4. Which of the following is not a recognized extrahepatic manifestation of *hepatitis C virus* infection?
   A. Cryoglobulinemia
   B. Increased risk of myocardial infarction
   C. Membranoproliferative glomerulonephritis
   D. Vasculitis
   E. Insulin resistance

5. Which one of the following statements about hepatitis E is FALSE?
   A. Outbreaks of hepatitis E tend to be from contaminated water.
   B. Cases of hepatitis E in the United States are rare.
   C. Hepatitis E infection becomes chronic in more than one-third of individuals.
   D. The detection of anti-HEV IgG and IGM is diagnostic of infection.
   E. Infection with *hepatitis E virus* during pregnancy is associated with high mortality rate.

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# Liver Abscess

## Fever with Right Sided Abdominal Pain

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**Learning Objectives**

- Describe the clinical presentation and risk factors for the development of liver abscess
- Understand the pathogenesis of suppurative liver infections
- List the microbiologic etiologies known to cause infections of the liver parenchyma
- Develop an appropriate treatment and management plan for a patient found to have a liver abscess

## 14.1 Introduction to the Problem

Pyogenic liver abscesses are relatively infrequent infections. In the early 1900s, the most common underlying problem that led to the development of bacterial liver abscesses was pylephlebitis secondary to appendicitis. By the late 1900s, biliary tract disease had replaced pylephlebitis as the most frequent predisposing condition leading to bacterial liver abscesses. Disorders of the gallbladder and biliary tract continue to play the primary role in predisposing patients to parenchymal liver infections in developing countries today [1–6]. Liver abscesses arising in association with malignancies and their treatment have also increased in the last several decades. Not all bacterial liver abscesses arise from a contiguous intra-abdominal source. Hematogenous seeding of the liver during periods of bacteremia can also lead to the formation of liver abscesses. Patients who are found to have liver abscesses secondary to bacteremic seeding almost always have one or more easily identifiable predisposing risk factors such as thalassemia, sickle cell disease, poorly controlled human immunodeficiency virus infection, a primary immunodeficiency disorder (most notoriously chronic granulomatous disease), or a history of intravenous drug use. Bacteria are not the only cause of liver abscesses. Fungal liver abscesses occur among cancer patients who develop prolonged periods of neutropenia and among patients with severe primary and acquired immune deficiencies. Liver abscesses can also be caused by amoeba. A well-appreciated complication of acquiring *Entamoeba histolytica* carriage or gastrointestinal illness among travelers and individuals living in areas with unreliable access to clean drinking water is the development of liver abscesses.

## 14.2 Definitions

**Liver abscess** - A pyogenic infection of the liver parenchyma.

**Pylephlebitis** - Thrombophlebitis of the portal vein caused by an intra-abdominal infection.

**Trans-arterial chemoembolization (TACE)** - A minimally invasive procedure performed to restrict a tumor's blood supply. Tiny particles embedded with chemotherapeutic medications are injected directly into a tumor's primary feeding artery.

**Radiofrequency ablation** - A procedure in which tumor cells are eliminated using heat energy generated from a medium frequency (350–500 kHz) alternating current.

**Amoebic dysentery** - An intestinal infection caused by Entamoeba histolytica resulting in diarrhea that contains blood and mucous.

**Hepatosplenic candidiasis** - A rare condition that occurs secondary to hematogenous seeding of the liver parenchyma with the yeast *Candida albicans* (or related species) under conditions of severe immunosuppression.

## 14.3 Basic Concepts

### 14.3.1 The Incidence and Microbiologic Etiologies of Pyogenic Liver Abscesses

Across the world, the incidence of liver abscess varies from region to region. In North America, rates are comparatively low, with a reported incidence of approximately 2.3 cases per 100,000 hospital admissions [1, 2]. In the developed world as a whole, the reported incidence is 10-fold higher with liver abscess accounting for 1 in every 4500–7000 hospitalizations [7]. Bacteria, fungi, and the parasite *E. histolytica* are all known to cause liver abscesses.

Bacteria that are recovered from a substantial percentage of liver abscess fluid cultures include *Escherichia coli*; species of *Klebsiella*, *Enterococcus*, *Bacteroides*, *Fusobacterium,* and *Salmonella*; aerobic, anaerobic, and microaerophilic streptococci; and *Staphylococcus aureus*. Polymicrobial bacterial infection is not uncommon. Reports of liver abscesses caused by *Klebsiella pneumoniae* have been recognized with higher frequency for more than three decades, gaining increasing attention because of an unusually high rate of associated complications [8–11].

Historically, *E. coli* was the most common bacterial cause of pyogenic liver abscesses usually found in a setting of polymicrobial infection with a bowel or biliary source. By the mid-1980s, case reports of liver abscesses caused by *K. pneumoniae* began to emerge. *K. pneumoniae* has become particularly problematic in Asia where it accounts for between 50% and 73% of liver abscess cases, many of which are occurring is patients with diabetes mellitus [12–16]. Given the unusually high incidence of liver abscess occurring among the Asian population, a genetic predisposition to this particular pathogen has been suggested.

Anaerobic bacteria are normally present in the human gastrointestinal tract in very high numbers, but as a group, these bacteria are infrequently cultured from liver abscess fluid. Liver abscesses that form in association with pathology originating in the pelvis, colon, or appendix are more likely than others to yield growth of an anaerobe, but almost always in combination with one or more aerobic bacteria. The most common anaerobes to cause human infection, including liver abscesses, are members of the *B. fragilis* group. *Fusobacterium necrophorum*, the primary cause of Lemierre's syndrome, a

serious anaerobic infection of the neck that is associated with internal jugular vein septic thrombophlebitis, is also occasionally isolated in pure culture from liver abscess fluid. *Clostridium perfringens* has also been reported as a rare cause of liver abscess [17].

Hematogenous seeding of a distal site such as a bone, a joint, the meninges, the spleen, or the liver occurs in up to 15% of cases of bacteremia caused by either *S. aureus* or a *Salmonella* species explaining the presence of these organisms in some liver abscesses. Predisposing conditions for the development of *S. aureus* liver abscess include chronic granulomatous disease and injection drug use. *Salmonella* species liver abscesses are more likely to occur in patients with underlying hemoglobinopathies. Similarly, *Candida* species abscesses occur secondary to fungemic seeding of the liver during periods of chemotherapy-associated neutropenia in patients with cancer. Unlike bacterial liver abscesses, which occur as lesions with one to three or four foci, *Candida* species infections occur as micro-abscesses present throughout the liver and the spleen and are more accurately referred to as "hepatosplenic candidiasis" rather than a candida liver abscess. Table 14.1 provides a summary of the pathogens associated with liver abscesses and their known predisposing conditions.

## 14.4 Predisposing Risk Factors for the Development of Liver Abscesses

Between 30% and 50% of patients who develop hepatic abscesses are diabetic, clearly identifying diabetes mellitus as its most common risk factor [17, 18]. Hyperglycemia alters neutrophil metabolism, chemotaxis, and phagocytosis, weakening innate immune defense against infection. Preexisting liver cirrhosis, malignancy, or immunosuppressive disorders also elevate the risks for liver abscess development. Cirrhotics, for example, are 15 times more likely to develop liver abscesses than noncirrhotics [6, 19, 20]. Surgical procedures used in the treatment of hepatocellular carcinoma, such as **t**ranscatheter **a**rterial **c**hemo**e**mbolization (**TACE**) and **r**adio**f**requency **a**blation (**RFA**), also carry a higher risk for liver abscess formation with complication rates of 1.4% and 0.5%, respectively [21]. The incidence of liver abscess is also increased in those with diverticular disease compared to those without it [20, 22].

Nonmetastatic colorectal cancer has also been associated with hepatic abscess formation likely from local erosion of the mucosa by the tumor, facilitating the entry of colonic bacteria into the bloodstream with subsequent hematogenous seeding of the liver [18, 23, 24]. Similarly cases of liver abscess have been reported following polypectomy [25].

Any condition that substantially increases the risk for bacteremia or fungemia can lead to hematogenous seeding of the liver with subsequent formation of an abscess. Such conditions include, but are not limited to, primary and acquired immunodeficiency, anatomic and functional asplenia, cancer, organ transplant recipient, presence of an indwelling central venous catheter, dependency on hyperalimentation, and intravenous drug use. Factors associated with higher mortality include male gender, underlying malignancy, the presence of multi-organ failure, and rupture of the liver abscess into the peritoneal space [21].

## 14.5 Pathogenesis of Hepatic Abscess Formation

There are several routes by which infecting organisms can reach the liver, including retrograde seeding from pathogens entering the biliary tree; direct extension of infection from another intra-abdominal source; hematogenous seeding via the portal vein or hepatic artery, as occurs for most *S. aureus* infections; and direct inoculation via penetrating trauma. In the pre- and early antibiotic era, the pylephlebitis associated with infection of abdominal viscera, primarily the appendix, was the most common source of liver abscess formation. Appendicitis rarely leads to the formation of liver abscess now because of the standard practice of early empiric broad-spectrum antibiotic use.

Presently, the most common route for infection of the liver is by retrograde migration of pathogens from the biliary tree to the liver parenchyma. Biliary tract infections occur predominantly in the setting of obstruction from gallstone disease, malignancy, or stricture, leading to proliferation of bacteria in the biliary tract, ascending cholangitis, and hepatic invasion. Contiguous spread from other intra-abdominal infections such as diverticulitis, colitis, and pancreatitis also occurs, although an obvious source remains elusive in a significant number of individuals. Patients with primary hepatocellular carcinoma tend to develop areas of central necrosis, which can then become infected with bacteria. Liver cancer may also cause biliary obstruction, which can in turn predisposes the patient to ascending cholangitis with subsequent formation of liver abscesses. Alternatively, liver abscess can present as an initial manifestation of hepatocellular carcinoma and delay the diagnosis of the underlying malignancy. Abscesses that develop in this context usually have thickened walls with septations, portal thrombosis, aerobilia (gas bubbles in the biliary tree), and gas within the abscess [21].

Necrotic areas of the liver are particularly prone to infection, so any insult resulting in foci of liver necrosis is at risk for abscess formation. Surgical procedures performed on the hepatobiliary tree can disrupt the liver's blood supply, leading to areas of ischemic necrosis. TACE-induced areas of necrosis are particularly susceptible to infection, explained in part by the procedure's association with suppression of normal reticuloendothelial cell activity [26]. Arterial embolization can also result in areas of ischemic liver necrosis with

subsequent abscess formation. The role of antibiotic prophylaxis for the prevention of ablative procedure-related liver abscess formation remains unclear [27, 28]. Biliary strictures that impair or block the flow of bile are another known complication from surgical procedures used to treat liver cancer that increases the risk for developing liver abscesses.

## 14.6 Clinical Manifestations

Patients with liver abscesses usually present with fevers, chills, and right upper quadrant abdominal pain. Fever is the most common symptom, reported in 95% of cases [10, 29, 30]. Substantial hepatic tenderness may be present. Associated symptoms may include diarrhea, jaundice, right-sided pleural effusion, anorexia, nausea, or vomiting. Half of the patients may have no symptoms or signs to suggest liver involvement, presenting instead as fevers of unknown origin.

### 14.6.1 Complications

Rupture of a liver abscess into the peritoneal cavity is a life-threatening complication. Although spontaneous rupture of a liver abscess is rare, there is a higher incidence when *Klebsiella pneumoniae* is the infecting organism [30–32]. Other risk factors for spontaneous rupture in liver abscess include diabetes mellitus, large abscess size, thinned-wall abscess, and abscesses that show gas bubbles on imaging studies [32].

Systemic complications from liver abscess include bacteremia, septic shock, disseminated intravascular coagulation, acute renal failure, and acute respiratory failure. These sepsis-related clinical presentations typically occur prior to the identification of the hepatic source and are more common among those patients with liver abscess caused by *K. pneumoniae*.

Patients who develop bacteremia as a complication of liver abscess are at risk for seeding extrahepatic sites [33]. Meningitis is associated with high mortality. Endophthalmitis leads to subacute vision impairment that typically progresses to blindness despite aggressive treatment with intravenous and intravitreal antibiotics [34, 35, 36]. Patients with septic pulmonary emboli or empyema also have poor outcomes. Osteomyelitis, subcutaneous, or muscular abscesses also occur.

## 14.7 Diagnosis

Plain abdominal radiographs rarely assist in the diagnosis of liver abscess; however, abscess-associated air-fluid levels or portal venous gas can be seen. Liver ultrasonography is 96% sensitive in detecting liver abscess. The ultrasonographic appearance of a liver abscess is typically hypoechoic (Fig. 14.1), although hyperechoic signals can be seen. Computer tomography scanning is virtually 100% sensitive for the diagnosis revealing low attenuation signals surrounded by normal liver parenchyma and a characteristic rim enhancement after the administration of intravenous contrast material (Fig. 14.2).

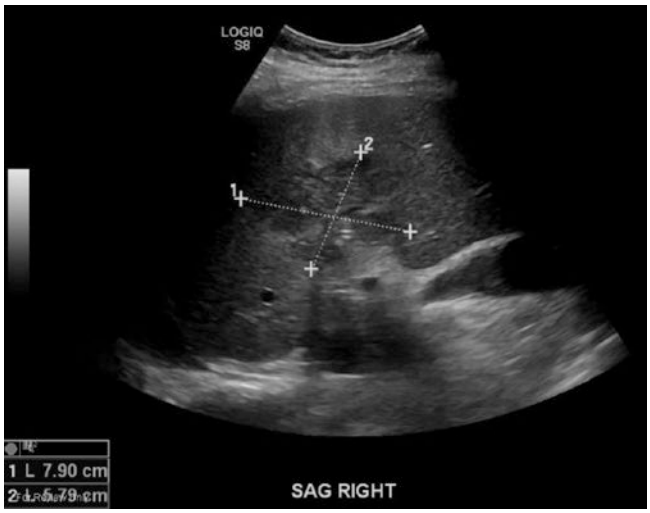


**Fig. 14.1** Shown are ultrasonographic findings of a large liver abscess demonstrating a heterogeneous, hypoechoic lesion involving the central portions of the anterior right hepatic lobe (identified by dotted lines used to measure the size of the lesion). (Image provided by Dr. Joseph Domachowske)

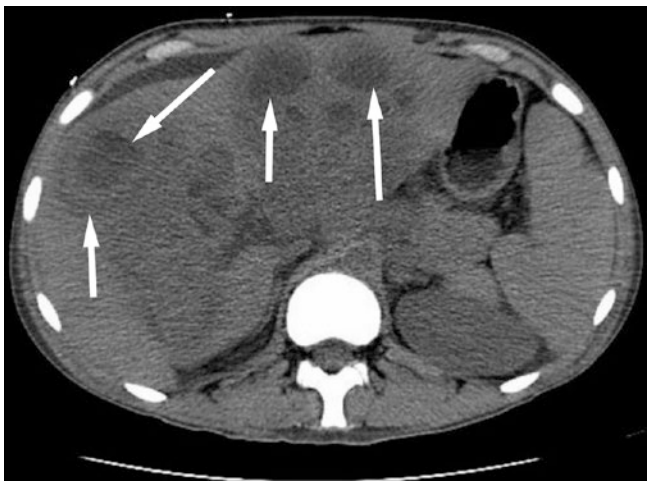

**Fig. 14.2** Shown is a contrast-enhanced computer tomography image of large multiloculated, peripherally enhancing collections with central areas of low attenuation consistent with the presence of multiple abscesses. Abscess fluid cultures were positive for *Staphylococcus aureus*. The patient's predisposing risk factor is a primary immune deficiency in neutrophil oxidative burst function called chronic granulomatous disease. (Image provided by Dr. Joseph Domachowske)

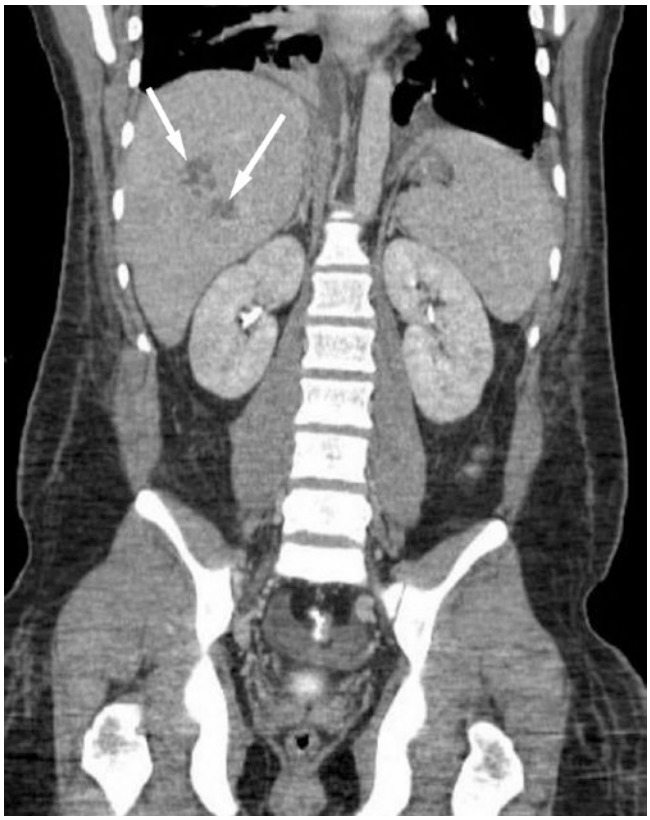

**Fig. 14.3** Axial magnetic resonance image of the same abscess shown in Fig. 14.1 (*arrows*). The hypodense areas represent the abscess collection. This image was performed in the absence of intravenous contrast, so the typical rim enhancement is not seen. Note the high resolution of this imaging technique. (Image provided by Dr. Joseph Domachowske)

Under circumstances where both ultrasonography and computer tomography scanning are nondiagnostic, magnetic resonance imaging (MRI) or contrast-enhanced ultrasonography (CEUS) can be used to assist in confirming the diagnosis. On MRI, liver abscesses appear hyperintense on T2-weighted images and hypointense on non-contrast T1-weighted images. Depending on the proteinaceous content of the liver abscess, some may demonstrate hyperintense signal on non-contrast T1-weighted images. These imaging techniques also play a role in image-guided needle aspiration to collect samples for diagnostic testing and during attempts at drainage (Fig. 14.3).

The single most reliable laboratory finding in patients with liver abscess is an elevated serum alkaline phosphatase, which is found in 70% of affected patients. Other common laboratory abnormalities seen include leukocytosis, low hemoglobin concentration (anemia), elevated erythrocyte sedimentation rate, elevated C-reactive protein, low serum albumin, elevated total bilirubin, and elevated serum hepatic transaminases. Right-sided pulmonary infiltrates with pleural effusion may be present.

Bacteremia or fungemia is seen in about 50% of all patients with liver abscesses. A positive blood culture can therefore identify the infecting pathogen and allow antimicrobial susceptibility testing to be performed. Collection of abscess fluid, however, is always important for both diagnostic and therapeutic purposes. Any of the bacteria or fungi listed in Table 14.1 can be cultured from blood or abscessed fluid. The causative pathogen may also raise suspicion for the presence of a previously unidentified risk factor and/or give insight into the most likely route and underlying source of infection. Microbiologic isolates of *K. pneumoniae* deserve additional attention because of their association with complications. *K. pneumoniae* isolates with a hypermucoviscous phenotype that are identified from the blood or fluid collected during abscess aspiration are highly suggestive of an invasive *K. pneumoniae* strain. Multiplex polymerase chain reaction (PCR) has also shown promise for the rapid detection of the *K. pneumoniae* serotypes known to be associated with hepatic abscess [37]. Patients with diabetes mellitus who present with *K. pneumoniae* bacteremia, endophthalmitis, meningitis, or other extrahepatic infections should be evaluated for the presence of an occult liver abscess.

On presentation, most patients have a single abscess, and most single abscesses involve the larger and better-perfused right lobe of the liver. Some reports indicate that abscesses caused by *K. pneumoniae* are more likely to appear as single abscesses with unilobar involvement [38] than abscesses caused by other gram-negative bacteria. Abscesses caused by *K. pneumoniae* also tend to have more loculations. The majority of abscesses do not exceed 10 cm in diameter [38–40]. With the etiologic shift to *K. pneumoniae* as the primary causative agent of liver abscess infections, there is an increased risk of gas-producing liver abscess especially in patients with uncontrolled diabetes mellitus [41–43]. *Klebsiella* species are facultative anaerobes capable of producing carbon dioxide gas as a result of glucose fermentation, especially under hyperglycemic conditions.

## 14.8 Management

A multidisciplinary approach is used to optimize the management of a patient with a liver abscess. The collection of abscess fluid is necessary for diagnostic purposes. The procedure used to collect infected material also serves a therapeutic role if a substantial amount of the infection can be drained at the same time. Consultation with an interventional radiologist and a general surgeon helps to identify the optimal approach for the procedure. If the procedure can be done in a timely fashion and the patient is stable, the first doses of empiric broad-spectrum antibiotics should, ideally, be administered after culture material is collected. For patients who are unstable or in circumstances where there is any delay in performing the procedure, antibiotic therapy should not be delayed.

Percutaneous needle drainage is preferred in most cases. Surgical drainage should be considered for abscesses of the left lobe of the liver, if percutaneous drainage fails including circumstances where the infecting material is too thick to be aspirated, if multiple foci of abscess are present or the solitary lesion is multiloculated, for patients with underlying biliary tract disease or cirrhosis, and for abscesses that have already ruptured [36].

The choice for empiric therapy should include a spectrum of activity against enteric gram-negative bacilli including *E. coli* and *Klebsiella* species, in addition to gram-positive cocci including *S. aureus* and *Streptococcus anginosus*. Including therapy that includes a spectrum of activity targeting anaerobic bacteria should be considered. Piperacillin with tazobactam or a carbapenem class antibiotic includes coverage for nearly all of the possible bacterial culprits, including most anaerobes. Vancomycin can be added if methicillin resistant *S. aureus* is being considered, and metronidazole can be added if *B. fragilis* group anaerobic infection is a concern. If sufficient information is available to determine that anaerobic infection is unlikely, a third or fourth generation cephalosporin or quinolone group antibiotic can be used. Antifungal therapy should be added if yeast (*Candida* species) or mold (*Aspergillus* species, among others) infection is likely to explain the clinical condition.

Empiric antibiotic therapy should be adjusted to targeted therapy as soon as complete microbiologic data are available from bacteria isolated from the abscess fluid or from blood cultures. It is important to remain mindful that cases that are complicated by metastatic infection of the meninges require antibiotic therapy that achieves adequate concentrations in the liver and in the cerebrospinal fluid. Uncomplicated liver abscess, for example, can usually be treated successfully with the placement of a simple pigtail catheter for drainage and medical treatment with intravenous cefazolin, a first-generation cephalosporin, since most isolates are susceptible. If the same infection were to be complicated by meningeal seeding, resulting in meningitis, treatment with cefazolin would *not* be appropriate since first-generation cephalosporins do not cross the blood-brain barrier. In this context, treatment with a third-generation cephalosporin (ceftriaxone or cefotaxime) is necessary even if the isolate is reported to be susceptible to narrower-spectrum cephalosporins by the microbiology laboratory.

The optimal duration of antibiotic treatment for liver abscess remains unclear, but does depend, at least in part, on the organism(s) identified, the absence or presence of complications, the extent of success in draining the fluid, and on host factors, such as the degree of underlying immunosuppression. Many experts recommend a minimum of 3 weeks of intravenous therapy, followed by 1–2 weeks of oral antibiotics [9].

*Entamoeba histolytica* infection is common in many tropical areas of the world. This single-cell protozoan parasite has a special proclivity to cause liver abscess and therefore must be considered in travelers and immigrants from developing countries. Most infections caused by *Entamoeba histolytica* are localized to the colon, where the pathogen is capable of causing a spectrum of illness ranging from asymptomatic shedding to fulminant colitis with severe bloody diarrhea (amoebic dysentery). Extraintestinal complications of intestinal amoebiasis occur when there is hematogenous spread of the amoebic trophozoites from the colonic mucosa via the portal vein. The majority of patients with amoebic liver abscess have no bowel symptoms, and stool microscopy is usually negative for the presence of *E. histolytica* trophozoites and cysts. Individuals can present with amoebic liver abscess months or even years after travel or residency in an endemic area, so a careful travel history is mandatory during the early assessment of all patients with hepatic abscesses.

The diagnosis of amoebic liver abscess is achieved by a combination of serologic testing and liver imaging. Diagnostic fluid aspiration from the lesion is not necessary. Formerly, such abscesses were described as solitary lesions of the right lobe of the liver, but modern imaging techniques show a high frequency of multiple abscess formation. Serologic testing for *E. histolytica*-specific immunoglobulin G is highly sensitive (>94%) and highly specific (>95%) for the diagnosis of amoebic liver abscess [44]. False-negative serological test results, however, can be obtained early during infection, but repeat testing 1–2 weeks later eventually returns a positive result. The successful use of an antigen detection enzyme-linked immunosorbent assay (ELISA) or PCR-based assay in patients with amoebic liver abscess suggests that these tests also play an important role in the diagnosis of extraintestinal disease [44, 45].

Metronidazole is the drug of choice for the treatment of amoebic liver abscess. A 10-day treatment course typically cures the infection. A second medication is also recommended to eradicate any residual intestinal amoebae. Available luminal amoebicides include diloxanide furoate, iodoquinol, and paromomycin. All three are generally well tolerated.

Case Study

Practical Examples

**Table 14.1** Pathogens associated with liver abscesses and their known predisposing risk factors

| Pathogens | Known predisposing risk factors |
|---|---|
| **Aerobic gram-negative bacilli** | |
| *E.coli*, *Proteus* species, *Pseudomonas* species, *Eikenella corrodens*, others | Biliary tract disease, appendicitis, pylephlebitis, cirrhosis, malignancy |
| *Klebsiella pneumoniae* | Diabetes mellitus, all of the above |
| *Salmonella* species | Underlying hemoglobinopathy, bacteremia, gastroenteritis, typhoid fever |
| *Yersinia enterocolitica* | Gastroenteritis, consumption of chitterlings |
| *Brucella melitensis* | Travel to or residence in endemic areas |
| **Anaerobic bacilli** | |
| *Bacteroides* species, *Fusobacterium species*, *Actinomyces* species, *Clostridium perfringens* | Pelvic abscess, biliary tract disease, appendicitis, pylephlebitis, cirrhosis |
| **Gram-positive cocci** | |
| Microaerophilic streptococci, *Enterococcus* species | Biliary tract disease, appendicitis, pylephlebitis, cirrhosis, malignancy |
| *Streptococcus anginosus* | Bacteremia |
| *Staphylococcus aureus* | Bacteremia, injection drug use, chronic granulomatous disease |
| **Fungi** | |
| *Candida albicans* and other yeasts | Fungemia, neutropenia from cancer chemotherapy, neonates receiving hyperalimentation |
| *Aspergillus species and other molds* | Fungemia, neutropenia from cancer chemotherapy, chronic granulomatous disease |
| **Parasites** | |
| *Entamoeba histolytica* | Travel to or residence in endemic areas |

## 14.9 Exercises

Please refer to the supplementary information section for answers to these exercises.

? 1. 50-year-old male with poorly controlled diabetes presents with fever and chills. He is a self-employed accountant who works from an office in his home. He has no pets and denies any travel history outside of the USA. His temperature is 39 °C, blood pressure is 90/68, and his pulse is 92 beats per minute. His physical examination fails to reveal an obvious source for his fever. Results of laboratory testing reveal a total leukocyte count of 14,800 cells/μl with 85% neutrophil, 8% band forms, and 7% lymphocytes. His hemoglobin is 9.2 g/dL. Serum hepatic transaminases are mildly elevated, with an AST of 60 U/L and an ALT of 72 U/L. Hemoglobin A1C is 11% (marked elevated). Blood cultures are collected, and empiric broad-spectrum antibiotics are started. Abdominal ultrasonography shows an echogenic, cystic mass in right lobe of liver. Of the following bacterial pathogens, the one that is most likely causing this infection is:

A. *Escherichia coli*
B. Entamoeba histolytica
C. Klebsiella pneumoniae
D. Pseudomonas aeruginosa
E. *Bacteroides fragilis*

2. Of the following options, the one that best explains the observed rise in the incidence of hepatic abscesses in the US population during the last decade is an increase in the:
   A. Number of people age 65 years and older living in the USA
   B. Use of transcatheter arterial embolization procedures
   C. Abuse of alcohol in the population
   D. Incidence of hepatocellular carcinoma
   E. Total number of abdominal surgeries performed each year

3. A 60-year-old man presents with right eye pain and blurry vision. He is being considered for hospital admission to ophthalmology service when you are asked to assess him. He explains that he has also had abdominal pain with fever and chills that preceded his visual symptoms. On physical examination, his vital signs are normal except for a temperature of 39 °C. You note significant right upper abdominal discomfort on palpation. Abdominal ultrasonography reveals a 4 cm hypoechoic mass in the right lobe of the liver suggestive of an abscess. In addition to arranging for a drainage procedure and starting treatment with intravenous piperacillin and tazobactam, which of the following is the most important to consider at this time?
   A. Adding gentamicin to the antibiotic regimen
   B. Serologic testing for *Entamoeba histolytica*
   C. Including intravitreal antibiotics in the treatment regimen
   D. Surgical exploratory laparotomy
   E. Surgical removal of the right lobe of the liver

4. Your patient has a solitary liver lesion that is 4 cm in diameter. On computer tomography scan, the lesion is hypodense with obvious rim enhancement seen after the administration of intravenous contrast. Following needle aspiration, treatment with a third-generation cephalosporin was started. The abscess fluid cultures grew *Klebsiella pneumoniae* susceptible to the prescribed antibiotic. Despite 48 h of therapy, the patient has had persistent high fevers and is complaining of worsening abdominal pain. Repeat imaging shows that the abscess has enlarged, now with suspicion of impending rupture. Of the following options, the best next step in management is:
   A. Percutaneous drainage
   B. Repeat needle aspiration
   C. Surgical exploratory laparotomy
   D. Switch the antibiotics to a carbapenem class drug
   E. Observation with repeat imaging in 24 h



## 14.10 Summary

Liver abscess is a relatively infrequent infection of the liver. When a predisposing condition can be identified, biliary disease is most common. Enteric gram-negative bacilli are the most common organisms isolated from abscessed fluid collections. In primary liver abscess, *K pneumoniae* has emerged as the predominant pathogen, with a worrisome syndrome of metastatic complications including meningitis and endophthalmitis. Abscesses caused by fungi should be considered in patients with severe immunosuppressing conditions. Individuals who travel to or reside in underdeveloped parts of the world are at risk for developing liver abscess caused by the amoeba, *E. histolytica*. The diagnostic evaluation and treatment for amoebic liver abscess differs from that of suspected bacterial disease, so a high index of suspicion and careful travel history are key to identifying this disorder. The diagnosis of liver abscess is made after careful review of imaging findings and laboratory test results, including the results of cultures performed on blood and on fluid obtained from the hepatic lesions(s). Optimal treatment involves a combination of drainage and the administration of systemic antimicrobials. Overall prognosis is fair, although the presence of comorbidities portends a higher risk for complications and/or death.

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# Infectious Gastroenteritis

## Diarrhea with Fever

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## 15.1 Definition

Acute gastroenteritis (AGE) is an illness caused by viral, bacterial, or parasitic infection of the intestinal tract. The World Health Organization defines AGE as a clinical syndrome characterized by increased stool frequency (e.g., 3 or more loose or watery stools in 24 h or a number of loose/watery bowel movements that exceeds the usual number of daily bowel movements by two or more), with or without vomiting or fever [1]. A change in stool consistency versus previous stool consistency is more indicative of diarrhea than stool frequency. Symptoms of AGE usually last less than 7 days and not longer than 2 weeks.

## 15.2 Pathogenesis

Diarrhea can be classified as noninflammatory, inflammatory, or invasive based on the effect of the enteric pathogen on the intestinal mucosa (Table 15.1).

The noninflammatory or secretory diarrheas are characterized by low-grade or no fever and diffuse watery nonbloody stools. Secretory diarrhea is caused by enterotoxin-producing organisms such as *Vibrio cholerae* and enterotoxigenic *E. coli*, viruses, and parasites such as *Giardia lamblia*. Cholera is characterized by severe watery diarrhea due to changes in ion secretion and absorption resulting from the action of cholera toxin on electrolyte transport in the gut. Viruses infect enterocytes causing villus blunting or shortening of the villi. There is a decrease in the number of cells making up the villi, reducing the overall absorptive surface for nutrient uptake and damaging intestinal enzymes on the villus tips which lead to increased carbohydrate in the intestinal lumen with resultant increased osmolarity of the intestinal contents with malabsorption. Infection with *Giardia lamblia* causes the loss of brush border absorptive surfaces and diffuses shortening of villi, leading to secretory diarrhea.

Inflammatory diarrhea is often characterized by high fevers (greater than 40 °C), bloody stools, severe abdominal pain, and smaller volume stools. This type of diarrhea is caused by two groups of organisms—cytotoxin-producing, noninvasive bacteria (e.g., enteroaggregative *E.coli*, enterohemorrhagic *E. coli*, and *Clostridium difficile*) or invasive organisms (e.g. *Salmonella* spp., *Shigella* spp., *Campylobacter jejuni*, *Entamoeba histolytica*). Infection with both types of organisms causes damage to the intestinal mucosa. The cytotoxin-producing organisms adhere to the mucosa, activate cytokines, and stimulate the intestinal mucosa to release inflammatory mediators. Invasive organisms, which can also produce cytotoxins, invade the intestinal mucosa to induce an acute inflammatory reaction, involving the activation of cytokines and inflammatory mediators. Invasive organisms, such as *Salmonella* spp., may cause enteric fever by penetrating the intestinal epithelium, where the organisms gain access to the lymphoid tissue and disseminate via the lymphatic or hematogenous route. Enteric fever is characterized by severe systemic illness with fever and abdominal pain.

## 15.3 Epidemiology

Acute infectious gastroenteritis is a major cause of morbidity and mortality worldwide. In the United States, prior to the introduction of rotavirus vaccine in 2006, AGE was responsible for more than 1.5 million outpatient visits, 200,000 hospitalizations, and 300 deaths per year [2]. Despite significant reductions in AGE after the introduction of rotavirus vaccine, there are still more than 105,000 hospitalizations annually among children <5 years of age in the United States alone [3, 4].

Viral gastroenteritis is the most common cause of diarrheal illness seen both in the emergency department and in general practice. Viral pathogens are more common among children <5 years old than among older children or adults. Acute viral gastroenteritis can be transmitted by asymptomatic carriers as well as by symptomatic patients before the onset of symptoms. Viral AGE is generally transmitted by the fecal-oral route. Illness usually begins 12 h to 5 days after



**Table 15.1** Gastrointestinal syndromes

| | Characteristics of the stool | Mechanism of diarrhea | Site of infection | Examples |
|---|---|---|---|---|
| Secretory or watery diarrhea | Copious<br>Watery<br>No blood<br>No pus | Noninflammatory (enterotoxin) | Proximal small bowel | *Vibrio cholerae*<br>Enterotoxigenic *E.coli*<br>*Rotavirus*<br>*Giardia lamblia* |
| Dysentery or colitis | Scant<br>Pus<br>Blood | Inflammatory (invasion or cytotoxin production) | Colon | *Shigella* species<br>*Campylobacter* species<br>*Entamoeba histolytica* |
| Enteric fever | Often no diarrhea | Penetrating into the bloodstream | Distal small bowel | *Salmonella typhi*<br>*Yersinia enterocolitica* |

exposure and generally lasts for 3–7 days. Viral pathogens are detected more commonly during the winter months.

Bacterial enteritis typically affects adults and children older than 2 years of age and occurs through oral-fecal contamination and after exposure to poultry, other farm animals, or contaminated meat. Bacterial pathogens are detected more commonly during the summer months.

## 15.4 Etiologies of Infectious Gastroenteritis

There have been few comprehensive studies of the etiology of AGE in the United States [5–8]. Diagnostic testing available in clinical laboratories in the past was limited and the tests available had limited sensitivities for many of the enteric pathogens, especially those that more commonly infect children. With the recent development of molecular diagnostic tests that detect multiple enteric pathogens, it is now possible to characterize the etiology of AGE among hospitalized children and other cohorts of interest more completely [9].

A large study using a molecular panel that detects 23 enteric pathogens conducted at a regional children's hospital provides insights into the current etiology of AGE among children in in the United States [10]. In this study a pathogen was detected in 52% of AGE episodes. The most commonly detected pathogens included diarrheagenic *E. coli*, *Norovirus*, and enteric *Adenovirus*. Multiple pathogens were identified from 15% of submitted specimens.

Before universal rotavirus immunization was adopted in the United States, approximately one half of all hospitalizations for acute nonbacterial gastroenteritis in children were caused by *Rotaviruses* [11]. Despite the marked reduction in *Rotavirus*, other viral pathogens are detected frequently and account for more than half of all pathogens identified in children <5 years old. Currently *Noroviruses* are the most important cause of nonbacterial acute gastroenteritis in all ages [12]. Other viral pathogens that have been proven to cause acute gastroenteritis are shown in Table 15.2.

In developed countries, bacterial pathogens account for 2–10% of cases of gastroenteritis [13, 14]. *Campylobacter* sp., *Salmonella* sp., *Shigella* sp., and enterohemorrhagic *E. coli* (EHEC) account for the majority of cases in the United States (Table 15.2). Cases of salmonellosis have been linked to exposure to farm animals, poultry, eggs, and household pets such as healthy-appearing turtles, snakes and lizards, and puppies or kittens with diarrhea. Campylobacteriosis cases can often be linked to exposure to farm animals, poultry, eggs, or consumption of raw milk. *Yersinia enterocolitica*, *Vibrio* sp. bacteria including *Vibrio cholerae* and non-01 cholera, *Aeromonas* sp., and *Plesiomonas* sp. are unusual etiologies of gastroenteritis in developed countries. *Yersinia enterocolitica* infections are often linked to the consumption of certain ethnic foods prepared using the intestines of pigs, especially during holiday times. Yersiniosis can cause mesenteric adenitis, mimicking the presentation of acute appendicitis, with or without symptoms of diarrhea. The diarrhea-causing *E. coli*, EIEC (enteroinvasive), and EPEC (enteropathogenic) are seen most often in developing countries (Table 15.3).

**Table 15.2** Infectious causes of acute gastroenteritis in the United States

| Viral | Bacterial | Parasitic |
|---|---|---|
| *Rotavirus* | *Campylobacter* spp. | *Giardia intestinalis* |
| *Norovirus* | *Salmonella* strains | *Cryptosporidium parvum* |
| *Astrovirus* | *E. coli* | |
| Enteric *Adenoviruses* (*Adenovirus* 40/41) | *Shigella* spp. | |
| *Sapovirus* | *Clostridium difficile* | |
| | *Yersinia enterocolitica* | |

**Table 15.3** Classification of *Escherichia coli* that is associated with gastroenteritis

| *E. coli* type | Epidemiology | Stool characteristics |
|---|---|---|
| Enterohemorrhagic or Shiga-like toxin-producing (EHEC or STEC) | Hemorrhagic colitis associated with the development of hemolytic uremic syndrome | Bloody or non-bloody |
| Enteropathogenic (EPEC) | Acute and chronic endemic and epidemic diarrhea in infants | Watery |
| Enterotoxigenic (ETEC) | Infantile gastroenteritis in developing countries and traveler's diarrhea in all ages | Watery |
| Enteroinvasive (EIEC) | Diarrhea with fever in all ages | Bloody or non-bloody; dysentery |
| Enteroaggregative (EAEC) | Acute and chronic diarrhea in infants | Watery, occasionally bloody |

Up to 35% of individuals who travel to developing countries may experience bouts of diarrhea during or immediately following the trip. Most cases occur within the first 2 weeks of travel and last about 4 days. Regions of travel associated with the highest risk are Africa, South Asia, Latin America, and the Middle East. Bacteria are the most frequent cause of traveler's diarrhea, and enterotoxigenic *E. coli* is the most commonly identified pathogen.

Parasitic causes of gastroenteritis are uncommon in healthy children in the United States accounting for 1–8% of cases of gastroenteritis. Parasitic infections occur more

frequently in recent immigrants, travelers, and backcountry campers, those with exposure to farm animals, and immunocompromised patients. *Giardia lamblia* and *Cryptosporidium parvum* infections are the most common causes of parasitic disease in the United States (Table 15.2).

## 15.5 Clinical Presentation

Non-bloody diarrhea, vomiting, and fever are the most common findings in patients with viral gastroenteritis. However the clinical presentation of bacterial gastroenteritis may overlap with viral disease and the two are often clinically indistinguishable. Clinical features that suggest bacterial gastroenteritis include age greater than 2 years, gross blood or mucus in the stool, high fever (greater than 40 °C), tenesmus, associated seizures, severe abdominal pain, and smaller volume stools. Patients with bacterial AGE are more likely to have identified risks such as international travel, exposure to poultry or other farm animals, and consumption of processed meat. Parasitic infections typically cause watery diarrhea, abdominal cramping, vomiting, and low-grade fever. Parasitic infections frequently cause more prolonged diarrhea often lasting well beyond 14 days.

## 15.6 Complications

As a direct consequence of diarrhea and vomiting:

- Hypovolemia/dehydration: Severe dehydration may lead to shock, multi-organ dysfunction, and death. Dehydration occurs predominantly among very young children and the extreme elderly. Young children are more susceptible to dehydration than older children because they have a higher body surface-to-volume ratio, a higher metabolic rate, and lower fluid reserves. Extreme elderly patients may be unable to maintain adequate oral hydration independently.
- Electrolyte abnormalities and acid-base disturbance including hypernatremia, hyponatremia, hypokalemia, and metabolic acidosis.
- Lactose intolerance due to damage to mature enterocytes on small intestinal villi containing lactase is uncommon.
- Irritant diaper dermatitis.

Other complications are shown in Table 15.4.

**Table 15.4** Complications of infectious gastroenteritis

| Complication | Associated etiologic agent(s) |
|---|---|
| Bacteremia | *Salmonella* spp., *Yersinia enterocolitica* |
| Seizures and fever | *Shigella* spp. (more common), *Campylobacter* and *Salmonella* spp. less likely |
| Encephalopathy | *Shigella* spp. (more common), with *Salmonella* sp. less likely |
| Extraintestinal infections | *Salmonella* sp. (more common), other bacteria less likely |
| Guillain-Barre syndrome | *Campylobacter jejuni* |
| Hemolytic-uremic syndrome | E. coli O157:H7 and other Shiga toxin-producing strains (STEC) |
| Meningitis | *Salmonella* spp. in neonates and extreme elderly |
| Reactive arthritis | *Salmonella* spp., *Shigella* spp., *Campylobacter* spp., and *Yersinia* spp. |
| Bowel perforation, toxic megacolon, secondary bacteremia | Any of the bacterial agents associated with invasive diarrhea; *C. difficile* |
| Pseudoappendicitis | *Yersinia enterocolitica* |

## 15.7 Clinical Evaluation

The evaluation of children with acute gastroenteritis frequently begins with a telephone call from the caregiver. The focus of the conversation should be to assess the child's fluid status and the possibility of severe illness or a condition other than acute gastroenteritis that requires specific therapy.

Indications for a medical visit include the following [15, 16]:

- Age under 6 months or weight < 8 kg (17 lbs. 10 oz)
- Temperature ≥ 38 °C for infants <3 months or ≥ 39 °C for children 3–36 months
- Visible blood in stool
- Frequent and large amounts of diarrhea
- Diarrhea for more than 7 days or persistent vomiting
- Caregiver's report of symptoms of moderate to severe dehydration
- Multisystem compromise, cardiovascular instability (refer directly to the emergency department)
- Inability of the caregiver to administer or failure of the child to tolerate or respond to oral rehydration therapy at home
- Underlying immunodeficiency or condition complicating the treatment or course of illness, such as malnutrition, diabetes mellitus, or other metabolic diseases
- Social circumstances that make telephone assessment unreliable

The history and examination of children with symptoms and signs of gastroenteritis should focus on the following:

- Dehydration Assessment

The goal is to provide a starting point and determine the necessary intensity of intervention. Acute changes in body weight are the best measure. Decreased blood pressure is a late finding

**Table 15.5** Clinical dehydration scale (CDS) for the assessment of children

| | Points toward total assessment score | | |
|---|---|---|---|
| | 0 | 1 | 2 |
| General appearance | Normal | Thirsty, restless, or lethargic but irritable when touched | Drowsy, limp, cold, sweaty, or coma |
| Eyes (periorbital skin turgor) | Normal | Slightly sunken | Extremely sunken |
| Mucous membranes (tongue) | Moist | Sticky | Dry |
| Tears | Tears | Decreased tears | Absent tears |

Source [18]
A score of 0 represents no dehydration, a score of 1–4 represents some dehydration, and a score of 5–8 represents moderate/severe dehydration

**Table 15.6** World Health Organization assessment for dehydration

| | No dehydration (<5%) | Some dehydration (5–10%) | Severe dehydration (>10%) |
|---|---|---|---|
| Condition | Well, alert | Restless, irritable | Lethargic, unconscious |
| Eyes | Normal | Sunken | Sunken |
| Thirst | Drinks normally, not thirsty | Thirsty, drinks eagerly | Drinks poorly, not able to drink |
| Skin turgor/ capillary refill | Instant recoil | Delayed <2 seconds | Delayed >2 seconds |

Source [41]

of hypovolemia in children that corresponds to greater than 10% of fluids losses and heralds cardiovascular collapse. Prior guidelines from the Centers for Disease Control and Prevention (1992) [16] and the American Academy of Pediatrics (1996) [17] grouped patients in three subgroups:

- Mild dehydration (3–5% fluid deficit)
- Moderate dehydration (6–9% fluid deficit)
- Severe dehydration (>10% fluid deficit)

New studies indicate that the first signs of dehydration in young children might not be evident until a 3–4% fluid loss has occurred. Severe dehydration signs are usually not seen until the patient has experienced 9–10% losses. Updated recommendations group patients with mild and moderate dehydration together (Table 15.5) [18]. The World Health Organization (WHO) recommends a simpler system for use by both physicians and lay health workers, which classifies dehydration as none, some, or severe (Table 15.6).

A meta-analysis of 13 separate studies looking at individual signs and symptoms of dehydration found that only capillary refill times of more than 2 s, decreased skin turgor, and abnormal respiratory pattern (hyperpnea) had statistically and clinically significant positive and negative likelihood ratios for detecting dehydration in children [19].

- Evaluation of the child for other causes of diarrhea and/or vomiting that requires specific therapy and can be confused with AGE in the first day or two of symptoms (e.g., meningitis, acute abdominal processes, diabetic ketoacidosis, toxic ingestions).

Hospitalization should be considered for all children with acute gastroenteritis in the following situations [15, 20]:

- Signs of severe dehydration are present.
- Caregivers are unable to manage oral rehydration or provide adequate care at home.
- Factors present necessitating closer observation, such as young age, decreased mental status, or uncertainty of diagnosis.

## 15.8 Diagnostic Testing

The diagnosis of acute gastroenteritis is made clinically. Laboratory studies such as serum electrolytes, blood urea nitrogen, creatinine, or urinalysis are not routinely necessary. Microbiologic testing is likewise unnecessary in immunocompetent hosts with uncomplicated gastroenteritis; however, microbiologic testing should be considered for [15, 21]:

- Outbreaks of gastroenteritis, particularly in an institution with a closed population such as a hospital, child-care center, or school
- Cohorting and isolation of hospitalized patients
- Patients with underlying conditions such as immune compromise, malignancy, or inflammatory bowel disease
- Patients with diarrhea of 7 days' duration or longer
- Uncertain diagnoses

Blood cultures should be obtained from infants less than 3 months of age and from any patient with a toxic appearance or other clinical signs of sepsis, patients in whom enteric fever is suspected, those who are immunocompromised, and those who traveled to or have had contact with travelers from enteric fever-endemic areas [22].

Stool testing should be performed for *Salmonella* sp., Shigella sp., *Campylobacter* sp., *Yersinia* sp., and STEC in patients with diarrhea accompanied by fever, bloody or mucoid stools, severe abdominal cramping or tenderness, or signs of sepsis [22] since they may require antimicrobial therapy tailored to the infecting organism.

**Table 15.7** Pathogens detected by commercially available gastroenteritis multiplex polymerase chain reaction diagnostic panels

| Bacteria and bacterial toxins | Viruses | Protozoa |
|---|---|---|
| *Aeromonas* spp. | *Astroviruses* | *Cryptosporidium* spp. |
| *Campylobacter* spp. | Enteric *adenoviruses* 40/41 | *Cyclospora* spp. |
| *C. difficile* toxins A/B | *Noroviruses* | *Entamoeba histolytica* |
| *E.coli* O157 | *Rotaviruses* | *Giardia lamblia* |
| EAEC | *Sapoviruses* | |
| EPEC | | |
| ETEC toxins | | |
| *Plesiomonas shigelloides* | | |
| *Salmonella* spp. | | |
| STEC toxins | | |
| *Shigella* sp./EIEC | | |
| *Vibrio* spp. | | |
| *Vibrio cholera* toxin | | |
| *Yersinia enterocolitica* | | |

Historically, the microbiologic diagnoses of acute gastroenteritis have been made using microscopy, rapid antigen tests, stool culture, and, occasionally, real-time polymerase chain reaction (PCR) assays. A combination of these tests was often required because each type of test evaluates for different subsets of etiologies, and it's often impossible to distinguish between possible groups of infectious etiologies based on the clinical presentation alone. Recently, multiplex molecular assays have been developed for the detection of gastrointestinal pathogens directly from stool samples. These panels allow for the detection and identification of up to 23 pathogens with a laboratory turnaround time as short as 1 h (Table 15.7). Three multiplex real-time PCR assays are now licensed in the United States and are rapidly replacing traditional tests for the detection of enteric pathogens.

The major advantages of multiplex molecular assays are lower detection limits, higher sensitivity for common pathogens such as *Rotavirus* and *Shigella* spp., and the ability to detect uncultivatable pathogens such as *Noroviruses* [23]. Studies have demonstrated that the use of these multiplex panels will increase the positivity rates of enteric pathogens by two- to fourfold compared to conventional methods.

As use of these multiplex molecular assays becomes more commonplace, several new challenges will likely emerge for the clinician [23, 24]. First, these assays do not provide antimicrobial sensitivity data for bacterial organisms detected, so empiric antibiotic selection will need to be based upon prior known sensitivity patterns from the community or from the general literature. In addition these assays detect microbial DNA or RNA, not viable organisms, and therefore do not distinguish an active symptomatic infection from asymptomatic infection, colonization, or previous infection with continued shedding of the pathogen alive or dead. Pathogens such as *Norovirus*, *Rotavirus*, and *Salmonella* spp. have been shown to be present in the stool of asymptomatic individuals or shed for long periods following the resolution of disease and may be detected in those settings as well as in symptomatic disease. Organisms such as EAEC, EPEC, and *Sapovirus* that have not been routinely tested for in the past may be detected. This may present a challenge for the clinician to interpret the clinical significance of test results showing the detection of these pathogens. The rate of reported coinfections is likely to increase with the use of these panels as well [25]. Insufficient data are available to guide clinicians on how to interpret such findings. Further research on use and interpretation of results from these highly sensitive assays is necessary [26–28].

## 15.9 Differential Diagnosis

Extraintestinal infections which may present with diarrhea and/or vomiting include staphylococcal and streptococcal toxic shock syndrome, meningitis, bacterial sepsis, bacterial pneumonia including legionellosis, urinary tract infection, and otitis media. These infections can usually be differentiated from acute gastroenteritis by their extraintestinal manifestations and/or early results of laboratory testing.

A number of noninfectious conditions can also present with symptoms that mimic those of infectious gastroenteritis. These include inflammatory bowel diseases, intussusception, appendicitis, food allergies, and lactase deficiency.

## 15.10 Clinical Management

The current mainstay of the clinical management and treatment for acute infectious gastroenteritis consists of oral rehydration and early reintroduction of food [15, 16, 20, 22, 29, 30]. Intravenous rehydration should be reserved for cases where oral fluid correction is not tolerated or when the severity of fluid losses has already led to impending hypovolemic shock.

The objectives of treatment include the following:

- Prevention of dehydration, if there are no signs of dehydration.
- Treatment of dehydration, when present.
- Prevention of nutritional sequelae, by continued feeding during and after diarrhea.
- Reduction of the duration and severity of diarrhea.

No specific antiviral therapy is available for viral gastroenteritis. Anti-infective options are available for the treatment

of bacterial and parasitic causes of gastroenteritis, but their use is not always indicated, frequently unnecessary, and, in some instances, should be specifically avoided. Symptomatic therapy for AGE with watery diarrhea and/or vomiting consists of replacing fluid losses and correcting electrolyte disturbances through oral and/or intravenous fluid administration.

### 15.10.1 Oral Rehydration Therapy

The American Academy of Pediatrics (AAP), the European Society for Pediatric Gastroenterology Hepatology and Nutrition (ESPGHAN), and the World Health Organization (WHO) all recommend oral rehydration solution (ORS) as the treatment of choice for children with mild-to-moderate gastroenteritis in both developed and developing countries, based on the results of many randomized, controlled trials and several large meta-analyses [16, 17, 19, 31].

Oral rehydration takes advantage of a specific sodium-glucose transporter (SGLT-1) in the intestinal brush border of the intestine to increase the reabsorption of sodium, which leads to the passive reabsorption of water. This transport remains intact even during severe gastroenteritis.

Rehydration solutions with low osmolarity and 1:1 ratio of glucose to sodium perform optimally. Solutions with high concentrations of glucose, such as juice, soft drinks, and sports drinks, have higher osmolarity thereby impairing optimal water/sodium transport from the gut into the bloodstream. Their use is discouraged during oral rehydration therapy, a point that should be used when discussing home strategies with parents who may assume otherwise.

WHO programs focusing on the treatment of dehydration with ORS have substantially decreased deaths from cholera and other gastroenteritis in developing countries. In the United States, the absence of cholera and the generally high level of nutrition and generous total body sodium levels in children have led to the development of a consensus for use of ORS containing less sodium than is currently included in the WHO-recommended ORS recipe. ORS available in the United States include Pedialyte, Infalyte, and Naturalyte. Both the WHO ORS and solutions containing less sodium have been shown to be safe and effective in treating dehydration associated with acute gastroenteritis.

The full benefits of oral rehydration therapy (ORT) have not been realized in the United States. One of the reasons for the low use of ORT is the ingrained, habitual use of intravenous therapy for most children who are hospitalized and many who are brought to the emergency department. Up to 49% of pediatricians report that they always use intravenous fluids to treat moderate dehydration and 33% use intravenous fluids to treat mild dehydration despite recommendations for the use of ORS in these clinical situations [24].

Hydration status in children can be assessed on the basis of easily observed signs and symptoms (Tables 15.5 and 15.6). Children with AGE who are not thirsty have moist mucous membranes, and wet diapers and tears are not dehydrated and do not require ORS. If the child is breastfed, the mother should be encouraged to breastfeed more frequently than usual and for longer at each feed. If the child is not exclusively breastfed, then oral maintenance fluids should be given at a rate of approximately 500 mL/day for children younger than 2 years, 1000 mL/day for children aged 2–10 years, and 2000 mL/day for children older than 10 years. In addition, ongoing fluid losses should be replaced with 10 mL/kg body weight of additional ORS for each loose stool and 2 mL/kg body weight of additional ORS for each episode of emesis (both for breastfed and non-breastfed children). A study by Freedman et al. found that patients with mild gastroenteritis and minimal dehydration experienced fewer treatment failures when offered half-strength apple juice followed by their preferred drinks compared with children given ORS [32].

Children who are mildly or moderately dehydrated should receive 50 to 100 ml/kg of ORS over 4 h and should be reevaluated often for changes in hydration. Additional ORS is given to replace ongoing losses (10 mL/kg body weight for each stool and 2 mL/kg body weight for each episode of emesis). After the initial rehydration phase, patients may be transitioned to maintenance fluids.

Children who are severely dehydrated with changes in vital signs or mental status require emergency intravenous fluid resuscitation. Hypotension is a late manifestation of shock in children. Mental status, heart rate, and perfusion, as assessed by capillary refill time, are better indicators of severe dehydration and incipient shock. After initial treatment with IV fluids, these children can be given oral rehydration.

Children who are vomiting generally tolerate ORS. ORS is contraindicated in the child who is obtunded or at risk for aspiration. When oral hydration therapy is complete, regular feeding should be resumed.

### 15.10.2 Early Refeeding

Early refeeding is recommended in managing acute gastroenteritis because luminal contents are a known growth factor for enterocytes and help facilitate mucosal repair following injury [33]. Introducing a regular diet within a few hours of rehydration or continuing the diet during gastroenteritis without dehydration has been shown to shorten the duration of the disease. Early refeeding has not been associated with increased morbidity such as electrolyte disturbance or a need for intravenous therapy.

Almost all infants with acute gastroenteritis can tolerate breastfeeding. For formula-fed infants, diluted formula does not provide any benefit over full-strength formula. Infants with the most severe gastroenteritis may require lactose-free formula until mucosal recovery, a healing process that is usually complete after 2 weeks.

Older children can consume a regular age-appropriate diet. Foods that contain complex carbohydrates (e.g., rice, wheat, potatoes, bread, and cereals), lean meats, fruits, and vegetables are encouraged. Fatty foods and simple carbohydrates should be avoided. No data suggests that a diet consisting of only bananas, rice, applesauce, and toast (the BRAT diet) speeds recovery from gastroenteritis, although those foods are appropriate to be included in a more varied diet. Exclusive use of the BRAT diet may lead to suboptimum nutrition. Lactose restriction is not usually necessary but may help to reduce diarrheal frequency in some children as an optional, short-term, and temporary dietary change during their convalescence.

### 15.10.3 The Use of Antimicrobials

Patients with uncomplicated gastroenteritis should not routinely be given antibiotics, including otherwise healthy individuals with salmonellosis who are older than 6 months of age. Antimicrobial treatment for gastroenteritis proven to be caused by bacteria other than *Salmonella* spp. or a parasite can be considered for patients who continue to have symptoms at the time the laboratory results become available, but is not always necessary [15, 20, 22]. Available data suggest that patients with hemorrhagic colitis secondary to EHEC, including E. coli O157:H7, who are treated with antibiotics are more likely to develop the complication of hemolytic uremic syndrome. As such, antibiotic use should generally be avoided in these patients unless they appear toxic or develop a secondary bacteremia while their colon is inflamed.

Certain patients do require antimicrobial therapy for infectious gastroenteritis because treatment reduces their risk for developing complications and accelerates their recovery. Individuals with suspected or confirmed sepsis, with extraintestinal spread of bacterial disease, who are younger than 6 months and found to have salmonella gastroenteritis, who are malnourished or immunocompromised with salmonella gastroenteritis, and those with *Clostridium difficile*-associated pseudomembranous enterocolitis, giardiasis, dysenteric shigellosis, dysenteric amebiasis, or cholera should receive antimicrobials [21]. Table 15.8 details antimicrobial treatment for specific pathogens causing infectious diarrhea.

### 15.10.4 Adjunctive Management

Antidiarrheal (i.e., kaolin-pectin) and antimotility agents (i.e., loperamide) are contraindicated in the treatment of acute gastroenteritis in children because of their lack of benefit and increased risk of adverse effects, including ileus, drowsiness, and nausea. Antimotility agents can, however, be particularly helpful as adjunctive therapy in adolescents and adults with traveler's diarrhea secondary to ETEC.

The antinausea and antiemetic drug ondansetron may be given to facilitate tolerance of oral rehydration in children older than 4 years of age and to help control nausea and vomiting associated with acute gastroenteritis in adolescents and adults. A review of seven randomized, controlled trials found that oral ondansetron reduced vomiting and the need for intravenous rehydration and hospital admission [34]. Over-the-counter antiemetics are not recommended due to associated drowsiness because that side effect impairs oral rehydration efforts.

Probiotics are supplements containing live microbes, usually bacteria or yeast that are sometimes used to prevent or treat symptoms of infectious diarrhea. Possible mechanisms of action for probiotics include synthesis of antimicrobial substances, competition with pathogens for nutrients, modification of toxins, and/or stimulation of nonspecific immune responses to pathogens that facilitate their clearance. Two meta-analyses support the use of probiotics (especially ***Lactobacillus***) in the treatment of acute infectious diarrhea in children [35, 36]. A recent meta-analysis found probiotics may be especially effective for the prevention of *C. difficile*-associated diarrhea in patients receiving antibiotics [37]. Despite the observation that probiotics help to prevent *Clostridium difficile*-associated diarrhea (CDAD), there is no evidence that they can be used effectively to treat CDAD or that they provide any added benefit as adjunctive therapy when combined with standard antibiotic treatment regimens.

## 15.11 Prevention of Infectious Gastroenteritis

Prevention remains a key strategy for reducing the overall burden of infectious gastroenteritis. Effective strategic measures shown to prevent the spread of enteric pathogens include proper sanitation methods for food processing and preparation, sanitary water supplies, pasteurization of milk, proper hand hygiene, sanitary sewage disposal, exclusion of infected people from handling food or providing health care, and exclusion of people with gastroenteritis from use of public recreational water facilities including swimming pools, lakes, and ponds.

Eggs and other foods of animal origin should be cooked thoroughly. Raw eggs and food-containing raw eggs should not be consumed. Hand hygiene after handling raw poultry, washing cutting boards and utensils with soap and water after contact with raw poultry, avoiding contact of fruits and vegetables with the juices of raw poultry, and thorough cooking of poultry are critical. Thorough hand hygiene after having contact with human or animal feces, particularly from puppies and kittens with gastroenteritis, is important and makes good common sense.

The single most important intervention that can be used to minimize fecal-oral transmission in at-risk areas such as restaurants, medical office settings, hospitals, schools, child-care facilities, community gatherings, campgrounds, fund

**Table 15.8** Antimicrobial treatment of bacterial gastroenteritis

| Bacterial pathogen | Who to treat | Recommended therapy | Alternative therapy | Comments |
|---|---|---|---|---|
| *Aeromonas hydrophila* | Those who remain symptomatic | Ciprofloxacin for 5 days or azithromycin for 3 days | TMP/SMX for 5 days | Not all strains produce enterotoxins or diarrhea |
| *Campylobacter jejuni* (and other species) | Children with dysentery | Erythromycin for 5 days or azithromycin for 3 days | Doxycycline or ciprofloxacin | Early treatment shortens the duration of illness and prevents relapse |
| *Clostridium difficile* (antibiotic-associated colitis) | Moderate to severe cases<br>All immunocompromised patients | Oral metronidazole or oral vancomycin for 7 days | Relapse: several options including oral vancomycin taper and fecal transplant | Vancomycin more effective for severe disease |
| Enterohemorrhagic *E. coli* (EHEC, STEC, *E. coli* O157:H7) | Not recommended<br>May increase the risk of hemolytic uremic syndrome (HUS) | Only for patients who appear toxic or are bacteremic | Antibiotics, if used, should be based on susceptibility results of the pathogen | Antibiotics have not been shown to decrease illness severity |
| Enteropathogenic *E. coli* (EPEC) | Those who remain symptomatic | Neomycin for 5 days (intraluminal agent, not absorbed) | None | Most strains are not toxogenic or invasive<br>May cause prolonged postinfectious diarrhea |
| *Salmonella* spp., non-typhoid strains | Patients at risk for invasive disease<br>Enteric fever | Susceptible strains use azithromycin for 3 days, cefixime for 5–7 days, or TMP-SMX for 14 days | Ceftriaxone or ciprofloxacin for resistant strains; 5-day course | Not indicated for noninvasive AGE with nontyphoidal strains<br>May prolong carriage |
| *Salmonella typhi*<br>Cause of typhoid fever | All patients, symptomatic or not | Susceptible strains use azithromycin or ceftriaxone for 5 days, cefixime for 14 days, or TMP-SMX for 14 days | Ciprofloxacin for 5 days | Increasing cephalosporin resistance being described |
| *Shigella* spp. | Those who remain symptomatic | Susceptible strains use cefixime for 5 days, azithromycin for 3 days, or ciprofloxacin for 3–5 days | Alternatives for susceptible strains use TMP-SMX for 5 days or ampicillin (not amoxicillin)<br>Ceftriaxone for 2–5 days for resistant strains | Shortens the duration of diarrhea<br>Eradicates the organism from the stool<br>Resistance to antibiotics is common |
| Traveler's diarrhea (ETEC) | Those who remain symptomatic | Azithromycin or cefixime or ciprofloxacin for 3 days | Rifaximin for those 12 yrs. and older, TMP-SMX | Most illnesses brief and self-limited<br>Resistance increasing worldwide; check country-specific susceptibility data |
| *Vibrio cholerae* | Confirmed or suspected case by travel history | Doxycycline or furazolidone for 3 days | Ciprofloxacin or TMP-SMX (if susceptible) | Close attention to replacement of losses |
| *Yersinia enterocolitica* | Severe disease or immunocompromised host<br>Not necessary for mild disease in healthy patients | TMP-SMX or ciprofloxacin | Ceftriaxone or gentamicin | High rates of resistance to ampicillin |

TMP/SMX is trimethoprim plus sulfamethoxazole

raising events involving the preparation of food and drink, and picnic settings is frequent hand hygiene measures combined with staff training and monitoring of staff procedures, where appropriate. Hand hygiene using alcohol-based sanitizers can be helpful in many settings but should not be used to clean hands that are visibly soiled and do not reduce transmission of *C. difficile* spores or non-enveloped viruses such as *Norovirus*, *Rotavirus*, or *Adenoviruses*.

### 15.11.1 Vaccines

The prevention of acute gastroenteritis through immunization is now available for some enteric pathogens. Two oral rotavirus vaccines, a monovalent attenuated human rotavirus vaccine and a pentavalent bovine-human reassortant vaccine, are now available for use in many parts of the world, including the United States [38, 39]. In the years following their introduction in the United States, vaccine use reduced the burden of rotavirus-related hospitalizations by 60–93% depending on overall vaccine coverage, age group studied, and the specific *Rotavirus* season evaluated. Reductions in all-cause gastroenteritis or diarrhea-related hospitalizations, emergency visits, and outpatient/physician office visits have also been observed [40].

Vaccines for cholera and typhoid fever have been developed for use in countries where these diseases are endemic or epidemic. Research is also underway to develop vaccines for other pathogens such as *Norovirus* and *C. difficile*.

## 15.12 Exercises

Please refer to the supplementary information section for answers to these exercises.

| Complications | Etiologies |
|---|---|
| 1. Pseudoappendicitis | A. *Campylobacter jejuni* |
| 2. Seizures and fever | B. *E. coli* O157:H7 |
| 3. Guillain-Barre syndrome | C. *Salmonella* spp. in neonates |
| 4. Hemolytic-uremic syndrome | D. *Shigella* spp. |
| 5. Meningitis | E. *Yersinia enterocolitica* |

Questions related to case scenarios:

**Case 1.** A 19-year-old young man presents with a history of diarrhea, abdominal cramps, and fever a few days after acquiring a pet turtle. What is the likely cause of his diarrhea?

A. *Campylobacter jejuni*
B. *E. coli O157:H7*
C. *Salmonella* spp
D. *Shigella* spp
E. *Yersinia enterocolitica*

**Case 2.** A 2-year-old child who attends day care presents with abdominal cramps and severe bloody diarrhea which has been present for 2 days. He has no fever. What is the likely etiology of his illness?

A. *E. coli 0157:H7*
B. *Giardia lamblia*
C. *Norovirus*
D. *Rotavirus*
E. *Salmonella* spp

**Case 3.** A previously healthy 32-year-old woman develops bloody diarrhea and fever. She visits the emergency department where a stool culture is obtained. Twenty-four hours later, the culture is reported as positive for *Salmonella* spp. She is still having diarrhea and low-grade fever. Of the following options, which treatment is preferred?

A. Ampicillin
B. Ceftriaxone
C. Ciprofloxacin
D. No antibiotic
E. Trimethoprim-sulfamethoxazole

**Case 4a.** A 6-month-old boy presents with a 2-day history of mild fever and vomiting and watery diarrhea with 8–10 stools per day. Vital signs include a temperature of 38 °C, pulse of 120 beats per minute, and respiratory rate of 40 breaths per minute. He is lethargic but arousable and has slightly decreased periorbital skin turgor, "sticky" mucous membranes, and decreased tears. What is this the child's clinical dehydration score?

A. 0
B. 3
C. 4
D. 5
E. 8

**Case 4b.** For the 6-month-old boy described in case 4a, which is the most appropriate *next* step in management?

A. Administer a bolus of intravenous fluid
B. Administer an oral rehydration solution
C. No therapy needed
D. Give a single dose of loperamide
E. Give a single dose of ondansetron

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## Recommended Additional Reading and Other Available Resources Including Clinical Practice Guidelines Grouped by Subtopic

### Management of AGE

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# Infections of the Urogenital Tract

Contents

# Urinary Tract Infections

## Fever, Dysuria and Flank Pain

*Matthew A. Mittiga*




J. Domachowske (ed.), *Introduction to Clinical Infectious Diseases*,
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**Learning Objectives**

- Recognize the common signs and symptoms of urinary tract infections.
- Understand the differences in risk for developing urinary tract infections in males and females.
- Review the techniques for optimal collection of specimens for urinalysis and culture.
- Gain familiarity with interpreting the results of a urinalysis and a urine culture.
- Recognize typical uropathogens.
- List antibiotics typically used to treat urinary tract infections.
- Describe when follow-up, imaging, or referral to a specialist is indicated.

## 16.1 Introduction

Infections of the urinary tract represent a substantial number of visits to primary care offices, urgent care clinics, and emergency departments. The anatomical location of the urinary orifice, combined with developmental and practical circumstances, frequently leads to bacterial contamination and infection of the urinary tract. Pyelonephritis is a straightforward clinical diagnosis in an adult with fever, flank pain, and dysuria; however, infants, young children, and some elderly or disabled adults cannot verbalize or describe symptoms that would traditionally be associated with a urinary tract infection. In such circumstance, the physician needs to maintain a high index of suspicion, especially in the presence of fever without source. An understanding of the epidemiology, clinical presentation, common uropathogens, and treatment protocols of UTI is essential for physicians in primary care roles.



## 16.2 Epidemiology

Urinary tract infections will occur in 3–5% of females and 1% of males, resulting in over 1.1 million visits to physicians annually. Hospitalization rates are greater for infants than for older children, adolescents, or adults. In girls who are prone to infection, the first UTI usually occurs by age 5, and 60–80% of first-time UTI sufferers will have a second occurrence within 18 months [1]. It has long been known that females are at greater risk for UTIs compared males, likely due to the anatomic structure of the lower urinary tract where females have a much shorter urethra than males. After the toddler age, there is an almost 10:1 female to male preponderance of UTI diagnoses into adulthood. In males prone to infection, the first UTI typically occurs during the first year of life [1]. Uncircumcised males are more prone to developing UTIs than circumcised males, likely due to the foreskin acting as a reservoir of bacteria near the urethral meatus.

Urinary tract infections tend to cluster around times of life that present particular challenges to normal voiding, specifically the time in diapers, during toilet training, and at sexual debut ("honeymoon cystitis"). Constipation may also develop during toilet training due to stool holding, increasing the risk of developing a UTI.

Urinary tract infections represent a significant cost burden to the health-care system, with inpatient admissions costing an estimated 180 million dollars a year [1].

Bacteria that originate in the intestine are the chief culprit for most UTIs. The anatomical proximity of the terminal alimentary canal and the urethral meatus leads to ample opportunity for urethral colonization. The vast majority of UTIs are caused by *Escherichia coli*, with *Klebsiella* and *Proteus* species also highly represented. Viral infections of the bladder may also occur. Adenoviruses are well known to cause cystitis. They should be considered when there is a hemorrhagic component to the bladder infection, especially when the urine culture fails to reveal a bacterial etiology.

## 16.3 Clinical Manifestations and Classification

Urinary tract infections are typically categorized as either infections of the upper urinary tract (the kidneys and proximal ureters) and the lower urinary tract (the bladder and urethra). In general, those of the upper tract will be more involved and have a higher potential for systemic illness and complications. Upper tract disease most commonly occurs from an ascending lower tract infection, so it rarely presents without a component of cystitis or urethritis.

*Pyelonephritis* is a bacterial infection of the renal parenchyma, renal pelvis, and ureters. This represents a more serious form of UTI and implications for complications and permanent renal injury, especially when it recurs or treatment is delayed. The patient with pyelonephritis is typically ill-appearing, uncomfortable, and febrile. Flank pain, abdominal pain, malaise, nausea, vomiting, and diarrhea are also common during episodes of pyelonephritis.

Infants with pyelonephritis may manifest symptoms that are more vague. Poor feeding, lethargy, and irritability are common. Fever without obvious source demands an evaluation of the urinary tract as one of the potential sources. Pyelonephritis is associated with intermittent bacteremia and may lead to sepsis if diagnosis and treatment are delayed. Sepsis that originates from a urinary source is sometimes referred to as "urosepsis."

*Cystitis* indicates inflammation or bacterial infection of the lower urinary tract, specifically the bladder, urethra, and their mucosa. It is generally associated with the classic symptoms of *dysuria*, urgency, frequency, and *hematuria*. Young children develop fever with isolated cystitis; however, the presence of fever may herald the ascent of the infection into the upper urinary tract in adolescents and adults.

*Urethritis* is the inflammation of the urethral mucosa. Urethritis presents with symptoms similar to cystitis, although often with low colony counts on urine culture. Urethritis and cystitis can also be present at the same time. Urethritis without cystitis should also be evaluated as a potential sexually transmitted infection (e.g., chlamydia or gonorrhea).

## 16.4 The Microbiology of Urinary Tract Infections

### 16.4.1 Bacterial Causes of Urinary Tract Infections

The most common cause of UTIs is the Gram-negative enteric bacillus, *Escherichia coli. E. coli* normally inhabits the human gastrointestinal tract, finding its way to the lower urinary tract through fecal contamination [2]. Once present in the lower urinary tract, it can ascend to the ureters and renal parenchyma to cause pyelonephritis. Other common causes of UTIs include various members of the *Enterobacteriaceae* family of bacteria such as *Klebsiella* species and *Proteus* species. *Proteus* species are noteworthy for their ability to produce a potent urease. Urease is an enzyme that hydrolyzes urea to form ammonia and carbon dioxide. *Proteus* species infections can therefore be associated with highly alkaline urine. Chronic alkalinization of urine promotes the formation of magnesium ammonium phosphate crystals ($NH_4MgPO_4 \cdot 6H_2O$) that precipitate in the kidney causing renal calculi [2] (Table 16.1).

*Pseudomonas aeruginosa,* a non-enteric Gram-negative bacillus, is an uncommon cause of community-acquired UTI but is frequently cultured from the urine of hospitalized patients and from patients with a long-standing history of recurrent infections that have required treatment with broad-spectrum antibiotics.

Gram-positive organisms are less frequent causes of UTIs. *Enterococcus* species, like the *Enterobacteriaceae*, inhabit the human gastrointestinal tract and are regular causes of UTIs [3]. *Staphylococcus saprophyticus*, a coagulase-negative staphylococcal species, causes cystitis in young females, but the identification of *Staphylococcus aureus* in a urine culture is more suggestive of a hematogenous source, perhaps complicated by the presence of a renal abscesses.

**Table 16.1** Bacterial uropathogens, Gram stain results, and important features

| Bacteria | Gram stain | Important features |
|---|---|---|
| *Escherichia coli* | Negative | Most common cause of UTIs<br>Originates from intestinal flora<br>Reduces nitrates to nitrites |
| *Klebsiella* species | Negative | Frequent cause of UTIs<br>Cause of some nosocomial UTIs associated with the presence of stents and indwelling urinary catheters<br>Reduces nitrates to nitrites |
| *Proteus* species | Negative | Urease producers<br>Alkaline urine pH 8 or higher<br>Associated with struvite stones<br>Can lead to staghorn calculi<br>Reduces nitrates to nitrites |
| *Pseudomonas aeruginosa* | Negative | Recurrent UTIs<br>Prior recipients of frequent antibiotics<br>Regular cause of nosocomial infections<br>More common with anatomic abnormalities<br>Does not reduce nitrates to nitrites |
| *Staphylococcus aureus* | Positive | Evaluate for a hematogenous source<br>Evaluate for renal or perinephric abscess<br>Does not reduce nitrates to nitrites |
| *Staphylococcus saprophyticus* | Positive | Cystitis in young women<br>Does not reduce nitrates to nitrites |
| *Enterococcus* species | Positive | Does not reduce nitrates to nitrites |
| *Streptococcus agalactiae* (group B streptococcus) | Positive | Can cause UTIs newborns from hematogenous seeding<br>Common cause of asymptomatic bacteriuria during pregnancy<br>Can cause cystitis during pregnancy<br>Does not reduce nitrates to nitrites |

### 16.4.2 Nonbacterial Causes of Urinary Tract Infections

Fungal infections of the urinary tract occur regularly, especially after surgical manipulation or instrumentation. *Candida albicans* is the most common fungal pathogen to cause infection in these circumstances. Patients who receive frequent or long-term broad-spectrum antibiotics are at risk for heavy colonization with *Candida albicans* and related yeasts. Foreign bodies, such as ureteral stents, are prone to contamination with these yeasts (or highly resistant bacteria), ultimately leading to infection and a need to remove the hardware. Mold infections of the genitourinary tract are only seen in patients with severe immunosuppression. Disseminated mold infections will often involve the kidneys as one of many organ systems affected.

Growth of a mold from a urine culture or the suspected presence of "fungal balls" on renal imaging should raise suspicion for disseminated fungal disease. Isolated involvement of the genitourinary tract would be highly unusual.

Viral pathogens can also affect the urinary tract. Adenoviruses are a very common cause of hemorrhagic cystitis. BK virus also causes urethritis and cystitis, sometimes with hematuria. BK virus is especially important to consider in renal transplant recipients because of its association with graft rejection.

### 16.4.3 Pathogenesis

Microbial virulence in UTIs has been studied extensively using uropathogenic *E. coli* as a model. Uropathogenic *E. coli* use surface fimbriae to adhere to the uroepithelium and resist the flushing action of a normal bladder void [4].

The association of constipation with UTI has long been established. While the exact mechanism of the relationship remains unclear, it is likely due, at least in part, to the overextended colon compressing the neck of the bladder. The partially compressed bladder cannot empty completely leading to post-void residual urine that can facilitate bacterial growth and lead to cystitis [5]. Some children with moderate to severe constipation have episodes of encopresis and fecal soiling due to liquid stool leakage around the hard impacted stool. The anogenital area, including the urethral meatus, becomes heavily contaminated with fecal bacteria that can multiply, thereby infecting the urethra. Ascending infection follows, first to the bladder and then to the ureters and kidney.

Spermicides present on condoms or applied intravaginally may also predispose to UTIs by altering vaginal flora and enabling bacterial colonization of the urethra. Abnormal voiding habits, urolithiasis, or anatomic abnormalities also increase the risk for developing UTIs. Introduction of foreign bodies into the urethra or bladder, sometimes performed for the purpose of sexual arousal, also predisposes to infection.

### 16.4.4 Clinical Presentation

The triad of dysuria, urgency, and frequency is the hallmark of cystitis in the adult population. The diagnosis can be more elusive in young children. Infants are unable to verbalize their complaints, so they typically present with vague, generalized symptoms. Fever without source is fairly characteristic and should trigger a thorough diagnostic evaluation, including a urine culture, in infants under 2 months of age. Temperature instability, poor feeding, lethargy, vomiting, and diarrhea are all seen in young infants with UTI. Neonates may develop a direct hyperbilirubinemia leading to jaundice. The presence of hematuria or malodorous urine is a more specific symptom and one that may be picked up by observant parents.

Toddlers and young children may be able to verbalize their discomfort and localize pain, somewhat facilitating the diagnosis. In this age group, complaints of abdominal or suprapubic pain, flank pain, or back pain should prompt an investigation for a UTI. Dysuria, urgency, frequency, or hematuria may be reported by the child directly. Sometimes symptoms are more vague, such as complaints of vulvar pain, pain when sitting, or simply the appearance of discomfort in the pelvic region.

Secondary enuresis that occurs in a previously toilet-trained child should also be investigated for potential UTI. While most instances of enuresis in toilet-trained children (especially nocturnal enuresis) are developmentally normal, patients who present to care for complaints of enuresis should have a urinalysis performed as part of their evaluation.

Parents will sometimes present to care with their child complaining of "strong smelling" urine or dark discolored urine, concerned that their child has developed a UTI. Careful evaluation of the urine is generally warranted. Foul smelling urine is not a firm predictor of UTI and may be a symptom of mild dehydration or a result of dietary intake [6]. Urinary frequency is another common complaint, prompting parental fear of diabetes since it is a well-known symptom of hyperglycemia. Performing a urinalysis and a random blood glucose level is an effective and efficient way to evaluate this condition.

Dysuria, or painful urination, is a key symptom of UTI but also occurs from other causes. Pain may arise from urethral irritation due to soaps, chemicals, or damp undergarments or secondary to chlamydia or gonorrhea. In both genders, overaggressive manipulation of the genital area during sexual activity, including masturbation, may irritate the urethral meatus and cause discomfort. Finally, children who have been sexually abused may present with complaints that seem, at first, to be related to a UTI. A complete medial history and comprehensive physical examination, including the anogenital area, is essential to determine whether physical or sexual child abuse could be contributing to the presenting complaints. All health-care providers and trainees are considered "mandated reporters" if they are considering the possibility that a child has been abused based on suspicions raised during the history and physical examination.

### 16.4.5 Diagnostic Considerations for Suspected Urinary Tract Infections

Once the clinical suspicion for UTI is raised, a prompt and reliable diagnosis is required so that appropriate treatment can be initiated. Fortunately, urine lends itself to relatively easy sampling and analysis, some of which can be done on site in a primary care office. Careful interpretation of laboratory data is mandatory to prevent incorrect diagnoses of UTIs and to avoid unnecessary antibiotic use.

Obtaining urine for analysis and culture can be done in several different ways. The optimal method of collection

depends on the patient's age, their comfort level, and the skill of the provider. Avoidance of contamination with skin flora is the primary goal. A midstream clean-catch specimen is generally preferred in older children and adults provided scrupulous care is taken to cleanse the area of the urethral meatus. After cleansing, the patient is instructed to start voiding into the toilet and, at midstream, capture urine into a sterile urine collection container without touching its top or inside walls. Collecting urine for culture from infants and children who are not yet toilet trained requires more skill. The gold standard of sterile urine collection is through suprapubic aspiration using a sterile needle attached to a syringe, to enter the bladder from the abdominal wall, just above the pubic symphysis. Gentle negative pressure on the syringe will allow urine to flow into the syringe when the needle enters the bladder. This procedure is most commonly used to collect urine for culture from neonates but is not practical or typically necessary in most circumstances outside of the hospital setting [7]. Instead, a catheterized urine sample is collected in most settings where midstream sampling isn't possible. Plastic urine bags that can be positioned with adhesive to collect urine from young infants when they next void spontaneously are available in most medical settings. These bags can be used to collect urine for measurement of urine output, if necessary, and to collect urine for some tests but is never considered an acceptable technique to collect a sample for urinalysis or urine culture. Contamination with skin flora is virtually guaranteed with a bag specimen rending laboratory test results impossible to interpret.

Providers comfortable in urinary bladder catheterization should be available in office settings where infants and young children are seen. Parents are sometimes hesitant to consent to this procedure, but an emphasis on the reliability of the data and the quick insertion and removal of the catheter helps to provide reassurance [8]. Meticulous attention to aseptic technique during bladder catheterization cannot be overemphasized. The goal is to collect urine free from bacterial contamination while avoiding the inadvertent introduction of bacteria into the urethra or bladder.

The urinalysis is a particularly useful tool for assessing a patient for possible UTI. Instruments used to perform urinalyses are relatively inexpensive and can be found in most primary care offices. Dipstick urinalyses use impregnated strips containing reagents that undergo a color change when exposed to urine containing various substances. The color change can be assessed visually by the technician by comparing the results to a standardized color chart or optically when the strip is placed into the urinalysis instrument. Results are typically available in seconds to minutes. The use of standardized instrumentation provides the more objective result [9].

Urine dipsticks reveal the presence and relative amounts of four parameters of interest when evaluating for the possible presence of a UTI, including leukocyte esterase, nitrites, hemoglobin, and total protein. Dipsticks also identify other parameters that are not directly related to infection, such as bilirubin and glucose concentrations.

Leukocyte esterase (LE) is an enzyme produced by white blood cells and, by proxy, indicates the presence and relative abundance of white blood cells in the urine. The urine dipstick is extremely sensitive in detecting LE, allowing detection on a 0 to 4+ scale. A positive LE test usually indicates that there are at least five white blood cells per high power field under microscopy. False-positive findings of LE may result from contamination of the urine with vaginal secretions or from flushing the prepuce with urine.

Nitrites are also detected on standard urine dipsticks. Many Gram-negative bacteria, such as *E. coli, Klebsiella* species, and *Proteus* species, express an enzyme that reduces nitrates to nitrites in the urine (Table 16.1). The presence of nitrites in the urine is, therefore, highly suggestive of the presence of such bacteria and, thus, suggestive of UTI. It is important to note that the presence of nitrites as detected by urine dipstick is *specific* for a UTI diagnosis, but that the test lacks sensitivity. Some pathogens known to cause UTIs do not reduce nitrates to nitrite and will give a negative nitrite result on urinalysis despite the presence of a UTI. In other words, a positive nitrite test is a compelling evidence that a UTI is present, but a negative nitrite test does not rule out the possibility of UTI [9].

The enzymatic conversion of nitrates to detectable concentrations of nitrites in the urine requires approximately 2 h of incubation [10]. Nitrites are, therefore, not detected in newly formed urine. Ideally a first-morning void is the best specimen for the evaluation of nitrites.

The dipstick urinalysis is also very sensitive at detecting the presence of heme, which is reported back as the detection of hemoglobin, the surrogate marker for the presence of blood. A positive hemoglobin result may indicate minor bleeding from irritation of the mucosa due to inflammation as a result of infection. Hemoglobin may also be present if there was a minor trauma during catheterization to obtain the specimen. Large amounts of hemoglobin in the absence of other indicators of infection should prompt further investigation for possible renal disease. Since the reagent for the hemoglobin test specifically tests for the presence of heme and myoglobin also contains heme, a positive dipstick "hemoglobin" result is, on occasion, the result of significant myoglobinuria (from muscle breakdown), rather than a result of blood in the urine. The presence of protein in the urine may indicate a heavy bacterial load or herald the presence of renal dysfunction. If hemoglobin is present, both the hemoglobin and the total protein reagents recognize it.

Clinical laboratories will perform a urinalysis with a microscopic evaluation if requested. Microscopy is performed on urinary sediment after the urine is centrifuged. It can be useful in evaluating for the presence of white and red blood cell casts or the presence of bacteria. Clinical laboratories that receive large numbers of specimens from children routinely perform "enhanced urinalysis." Here, results from the standard urinalysis and microscopic evaluation are reported. In addition, the laboratory performs a Gram stain

on urine that has not been centrifuged. The presence of leukocytes and bacteria on the unspun sample is highly predictive of a UTI in the pediatric population. The result also provides the Gram stain result and bacterial morphology a day or two ahead of the urine culture result. A typical report might state the presence of "3+ white blood cells and 4+ Gram-negative rods."

Urine culture is the gold standard used to diagnose a UTI. A positive urine culture identifies the pathogen and provides the results of antimicrobial susceptibility testing. Care must be taken when interpreting urine culture results, as the reliability and utility of the findings are directly related to technique used to collect the sample. Urine cultures are performed quantitatively explaining why they are one of the few results reported from the clinical microbiology laboratory as such. A known volume of the urine sample is plated onto solid culture medium in a manner that resulting colonies will be dispersed and amenable to counting. The technician reading the culture will count the number of colonies growing on the plate and report the number of colony-forming units per milliliter of urine after correcting for the inoculation volume. A typical preliminary laboratory report might state the presence of "80,000 colonies of lactose fermenting Gram-negative rods, antimicrobial susceptibility testing in progress." A final report from the same sample might read, "80,000 colonies of *E. coli*" with details about the organism's antibiotic susceptibility profile.

A UTI is confirmed based on substantial growth of bacteria from a reliably obtained urine sample. It is important to note that culture cannot distinguish between upper and lower urinary tract infection. Cultures growing several different bacterial species must be viewed with skepticism since such results are consistent with "urogenital flora" that has contaminated the sample, usually during the collection process. Polymicrobial UTIs can be seen in medically complex patients, but most polymicrobial urine cultures represent contamination and should simply be repeated with extra attention paid to the collection technique.



### 16.4.6 Imaging During the Evaluation of Urinary Tract Infections

Imaging studies are not routinely indicated for the initial diagnosis of an uncomplicated UTI. Patients who are systemically ill or who are suspected to have pyelonephritis based on their clinical presentation should undergo imaging to define the extent of their infection and to evaluate for possible complications.

Renal ultrasonography is reliable, fast, and does not require exposure to radiation or the use of intravenous contrast. Ultrasonography is an excellent tool for assessing the presence of anatomic abnormalities, abscess, obstruction, or hydronephrosis. Computed tomography scans are more sensitive than ultrasonography for the detection of pyelonephritis and its complications but require exposure to radiation and intravenous contrast.

### 16.4.7 Treatment

A host of antibiotic agents are available and appropriate for the treatment of UTI, in both oral and parenteral forms (Table 16.2). The choice of antibiotic agent and route of administration must take into account several factors, such

**Table 16.2** Representative antibiotic options for the treatment of urinary tract infections

| Antibiotic | Route of administration | Comments |
|---|---|---|
| Amoxicillin | Oral | Inexpensive<br>Narrow spectrum<br>Uropathogens often resistant<br>Ideal for treatment of isolates already known to be susceptible |
| Ampicillin | Intravenous | Inexpensive<br>Narrow spectrum<br>Uropathogens often resistant<br>Ideal for treatment of isolates already known to be susceptible |
| Amoxicillin/clavulanic acid | Oral | Inexpensive<br>Well-tolerated<br>Twice-daily dosing option<br>Broad-spectrum, including most uropathogens |
| Cephalexin | Oral | Inexpensive<br>Well-tolerated<br>Includes coverage for most *E. coli*<br>Other cephalosporin antibiotics also useful |
| Cefazolin | Intravenous | Inexpensive<br>Well-tolerated<br>Includes coverage for most *E. coli* |
| Ceftriaxone | Intravenous, Intramuscular | Once daily dosing<br>Able to be given intramuscularly<br>Very broad-spectrum, including most uropathogens |
| Trimethoprim-sulfamethoxazole | Oral, intravenous | Inexpensive<br>Twice-daily dosing<br>Emerging problems with resistance<br>Useful for β-lactam-allergic patients |
| Nitrofurantoin | Oral | Inexpensive<br>Twice-daily dosing<br>Concentrates in urine but not appropriate to treat pyelonephritis |

**Table 16.2** (continued)

| Antibiotic | Route of administration | Comments |
|---|---|---|
| Gentamicin | Intravenous | *E. coli* coverage<br>Narrow therapeutic window, therapeutic drug<br>Monitoring necessary<br>Oto- and nephrotoxicity concerns<br>Other aminoglycoside-class antibiotics also useful |
| Ciprofloxacin | Oral, intravenous | Other fluoroquinolone antibiotics also useful<br>Not used in children unless it's the only effective option<br>Very broad-spectrum, including most uropathogens |

as the patients overall clinical condition, prior history of UTI (including prior culture and susceptibility results), expected adherence to medication regimen, and cost.

Most antibiotics are naturally concentrated in the urine for elimination by the kidney. This results in excellent efficacy and potency for the treatment of most lower tract UTIs, but treatment for pyelonephritis needs to be tailored toward acceptable blood levels of antibiotics, since the renal parenchyma is involved. Some medications, such as nitrofurantoin, only reach effective levels when concentrated in the urine [10].

Generally, any patient who is sufficiently ill that they require hospitalization should receive intravenous antibiotics to treat their infection, at least to start. At the time of hospitalization, urine culture results may not yet be available, so empiric antibiotic choice should be tailored to include most uropathogens, particularly *E. coli*.

The combination of ampicillin and gentamicin remains a reliable empiric treatment option. Monotherapy with a cephalosporin-class antibiotic is also commonly used. Ceftriaxone has the added advantages of a once daily dosing interval and availability for intramuscular injection.

Historically, aminoglycosides such as gentamicin have also proven quite effective; however these medications must be given parenterally and have the potential to cause oto- and nephrotoxicity. Trimethoprim plus sulfamethoxazole can be used both in either the parenteral or oral formulation, but growing antimicrobial resistance to this agent must be considered if it is used for empiric therapy. If susceptibility testing of the pathogen is available, susceptible isolates are quite effectively treated.

Fluoroquinolones such as ciprofloxacin have excellent efficacy against *E. coli* and other enteric Gram-negative rods, including many isolates of *Pseudomonas aeruginosa*. Quinolone-class antibiotics are generally discouraged for use in children, although, at times, they may represent the only option for avoiding hospitalization for treatment with medications that can only be delivered by the intravenous route. Current pediatric guidelines state quinolone-class antibiotics should only be used for the treatment of *Pseudomonas aeruginosa* UTI or multidrug-resistant bacteria under limited circumstances and only after informed consent is obtained from parents [11].

Oral antibiotics are used to treat the vast majority of UTIs, including mild cases of pyelonephritis [12]. Empiric therapy, using an antibiotic that is likely to cover most common uropathogens, is initiated while awaiting culture and susceptibility testing results.

Empiric use of amoxicillin should generally be avoided due to increasing resistance patterns of community-acquired *E. coli*. Amoxicillin/clavulanic acid, however, is an acceptable empiric choice since the mechanism of resistance to amoxicillin alone is most often mediated by the production of a β-lactamase. Clavulanic acid is an effective inhibitor of many bacterial β-lactamases, allowing the amoxicillin component to function without being hydrolyzed [13]. Other β-lactam-class antibiotics such as the first-generation cephalosporin cephalexin and the third-generation cephalosporin cefdinir are highly effective when used empirically for the treatment of UTIs. β-lactam-allergic patients can be treated empirically with trimethoprim plus sulfamethoxazole, nitrofurantoin, or a fluoroquinolone. A quinolone-class antibiotic is sometimes the only practical option under circumstances of multi-class drug resistance, infections with *Pseudomonas aeruginosa,* or extensive histories of antibiotic allergies [14].

During antibiotic treatment, the pain associated with dysuria may be alleviated with increased hydration, frequent voiding, and/or sitz baths. Acetaminophen or ibuprofen may also be used for pain control. Phenazopyridine, an over-the-counter medication, also helps to provide some analgesia to the urinary mucosa. The use of cranberry juice has long been touted as an effective adjunct to medical treatment or prevention of UTI, but evidence is lacking to support the claim.

Antibiotic therapy for UTIs is typically given for 7–10 days. It is not necessary to repeat a urinalysis or culture if clinical improvement is rapid and complete. If symptoms do not improve or the patient's condition worsens, a repeat review of the urine culture and susceptibility results is in order. The prescribed medication and dosing regimen should be checked. The patient should be questioned directly about whether they have taken the medication as prescribed to be sure that they were able to secure the prescription and that they understand the directions for its use.

### 16.4.8 Special Circumstances

Individuals who have frequent UTIs should be referred for subspecialty consultation. Prior to this, the primary care provider should insure that measures have been taken to address common issues associated with attention to hygiene and dysfunctional voiding, including constipation. Patients who continue to have repeated UTIs despite addressing these

common problems should undergo a voiding cystourethrogram (VCUG). The most common disorder revealed by VCUG is vesicoureteral reflux (VUR), a condition by which urine is introduced back into the ureters by retrograde flow. A VCUG should also be performed under circumstances where the renal ultrasound indicates signs of hydronephrosis or parenchymal scarring [11]. A VCUG procedure involves the insertion of a catheter into the bladder by way of the urethra to inject radiopaque dye. The catheter is removed, and bladder emptying is visualized under fluoroscopy. A VCUG involves a substantial amount of radiation exposure, and therefore use should be limited to circumstances where suspicion for urinary reflux is high.

Young children with abnormal genitourinary anatomy, congenital bowel or bladder dysfunction, or other congenital abnormalities are at increased risk for developing recurrent and ultimately multidrug-resistant UTIs. Some of these patients may benefit from antibiotic prophylaxis keeping in mind that chronic long-term exposure to antibiotics may increase the risk for infections caused by highly resistant bacteria and for the new development of UTIs caused by *Candida albicans* and related yeasts.

## 16.5 Summary

Urinary tract infections are a common occurrence in primary care settings. Clinicians should have a high index of suspicion for UTI in febrile children, especially those without a clear source for the fever. UTIs may be mild, limited to the bladder and lower urinary tract, or they may develop to more severe disease involving the renal parenchyma. The definitive diagnosis of UTI rests on the proper interpretation of the urinalysis and culture results. Special attention should be paid to the manner in which the urine is collected with a focus on preventing bacterial contamination. While waiting on urine culture results, the urinalysis can help guide decisions regarding empiric antibiotic therapy. The choice of antibiotic agent should take into account local patterns of antibiotic susceptibility, the likely etiologic pathogen, and any special circumstances related to the patient. Most patients will recover fully from UTI, but some may require specialist consultation, especially those with underlying anatomic abnormalities.

## 16.6 Exercises

Please refer to the supplementary information section for answers to these exercises.

1. When deciding on an antibiotic to empirically treat a first-time urinary tract infection, the most important consideration should be:
   a. Cost of the medication
   b. A spectrum of activity that includes *E. coli*
   c. Oral versus intravenous formulation
   d. Dosing regimen of the medication

2. A 4-month-old male presents to the emergency department with complaints of fever, poor feeding, decreased wet diapers, and lethargy. As part of the diagnostic evaluation, urine studies are ordered. Which of the following techniques is most appropriate for collecting the urine specimen?
   a. An adhesive bag placed over the penis after the glans has been cleansed
   b. An absorbent gauze placed into the diaper
   c. A midstream clean-catch urine after the penis has been cleaned
   d. Bladder catheterization using aseptic technique

3. A urinalysis report shows the presence of 4+ leukocyte esterase and no nitrites. Which of the following is a correct interpretation of this laboratory test result?
   a. Urinary tract infection is unlikely since the nitrites are negative
   b. Absence of nitrites does not exclude a urinary tract infection
   c. This is likely an *E. coli* urinary tract infection
   d. This is asymptomatic bacteriuria

4. A 16-year-old female presents to a primary care office with complaints of dysuria, urinary frequency, and urgency. She is afebrile and otherwise healthy. She reports a history of one prior urinary tract infection 6 months ago. Which of the following studies is unnecessary?
   a. A voiding cystourethrogram
   b. A midstream clean-catch urine
   c. A urinalysis
   d. Review of the previous culture and antibiotic sensitivities

5. Which antibiotic is inappropriate for the empiric treatment of pyelonephritis?
   a. Ceftriaxone
   b. Cefazolin
   c. Ampicillin
   d. Nitrofurantoin

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# Human Papillomavirus Infection

## Clinically Silent Progression to Cancer
## Genital Warts

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**Learning Objectives**

- Understand the epidemiology of human papilloma virus (HPV) infection.
- Describe the clinical manifestations of HPV infection.
- Summarize the current recommendations for cervical cancer screening in the USA.
- Review the current HPV vaccine recommendations.
- List interventions that are associated with improved adolescent HPV vaccine coverage rates.

## 17.1 Definitions

**Condyloma acuminatum** – cauliflower-shaped anogenital papillomatous lesions caused by human papillomaviruses.

**Squamous intraepithelial lesions** – abnormal growth of squamous epithelial cells on the surface of the cervix.

**Juvenile recurrent respiratory papillomatosis** – HPV-associated squamous cell papillomas of the upper respiratory tract, most typically in and around the larynx.

## 17.2 The Basic Virology of Human Papillomaviruses

Human papillomaviruses (HPV) are small, non-enveloped, double-stranded DNA viruses that infect disrupted human epithelial cells resulting in either asymptomatic virus replication or the development of benign or malignant cellular changes [1]. Each HPV virion is composed of icosahedral capsids surrounding a circular DNA genome. The genome is divided into an early (E) region and a late (L) region. The early region includes the genes necessary for genome replication (E1 and E2) and virion assembly and release (E4), as well as genes involved in immune modulation (E5) and viral oncogenesis (E6 and E7). The late region of the genome includes the two genes that encode the major (L1) and minor (L2) structural capsid proteins [1, 2] (Fig. 17.1).

There are more than 120 types of HPV. Types 1, 2, and 4, like the majority of the other types, infect cutaneous or keratinized squamous epithelial cells and cause skin warts. In contrast, there are approximately 40 HPV types that infect the mucosa or nonkeratinized squamous epithelium. These virus types are stratified by their oncogenic potential. Low-risk, non-oncogenic HPV types, including types 6 and 11, can cause genital warts, laryngeal papillomas, and low-grade cervical cell abnormalities. High-risk, oncogenic HPV types, including types 16, 18, 31, 33, and 45, are associated with the development of anogenital and oropharyngeal cancers [3, 4]. Human papillomaviruses are one of seven viruses demonstrated to have clear oncogenic potential [▶ Call Out Box 17.1].

## 17.3 Epidemiology and Disease Burden

The vast majority of HPV infections are asymptomatic or subclinical making accurate determinations of infection prevalence challenging. Anogenital HPV infection is,

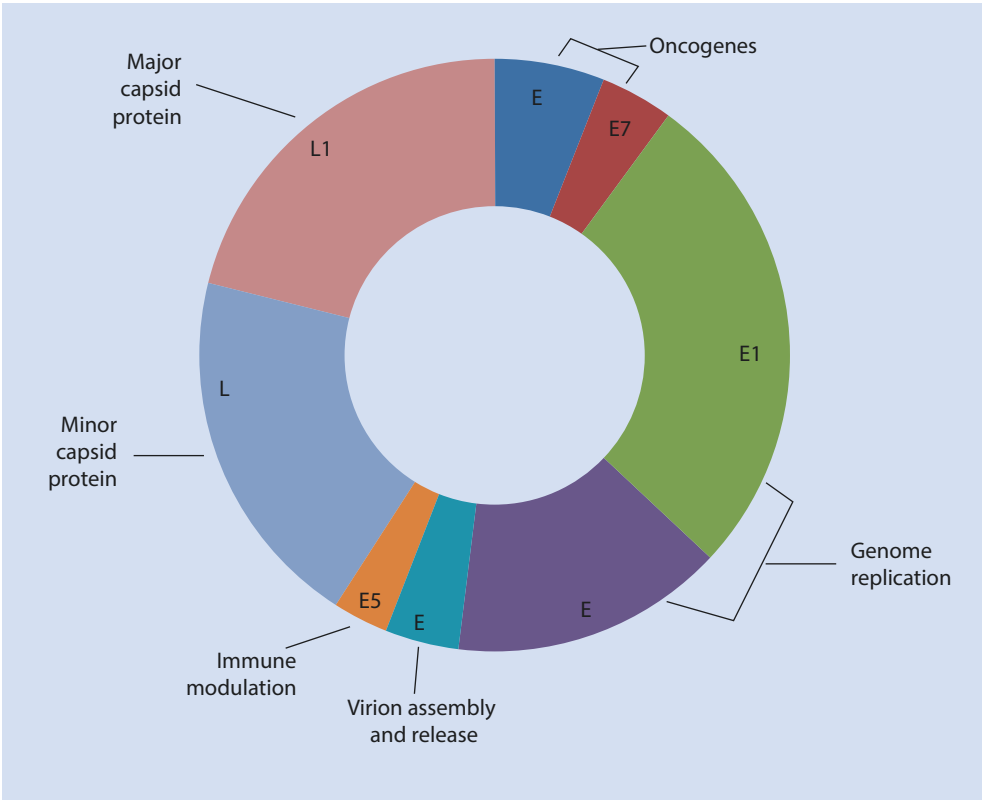


**Fig. 17.1** Shown is a schematic representation of the double-stranded circular HPV genome, including the early region (encoding E1, E2, E4, E5, E6, and E7) and the late region (encoding L1 and L2). The primary role for each of the gene products is also noted. E3 is not shown because it's a small gene that's only present in a few papillomavirus types. E3 is not known to be expressed as a protein and does not appear to serve any function

however, well appreciated as the most common sexually transmitted infection in the USA. Available data suggest that of the estimated 14 million new HPV infections that occur each year in the USA, half are affecting individuals between the ages of 15 and 24 years [3, 4]. In the USA alone, medical costs for HPV-associated disease, including routine cervical cancer screening and follow-up and treatment for cancers, anogenital genital warts, and recurrent respiratory papillomatosis, are approximately $8 billion annually [5].

HPV infection is spread primarily through direct sexual contact [6–9]. The single most important risk factor for acquiring HPV infection is the number of lifetime and recent sex partners, with newly acquired infections occurring soon after sexual debut [9–13]. More than 85% of sexually active adults will acquire HPV infection during their lifetime [10].

Nonsexual modes of HPV transmission are also well described. Nonsexual means of spread include direct skin-to-skin contact, skin-to-contaminated fomite contact, and vertical transmission from an infected mother to her child. Vertical transmission can occur in utero, but is much more likely to happen during delivery as the baby passes through an infected birth canal [6, 14]. Vertical transmission of HPV is responsible for most cases of recurrent juvenile laryngeal papillomatosis [15, 16].

Among US females, the prevalence of cervical HPV infection is estimated at 43%, with the highest prevalence described among 20–24-year-olds [17]. In contrast, the prevalence of HPV infection in US males is approximately 15%, with higher prevalence rates described among men who have sex with men (MSM) [18]. Visible anogenital warts are most common in individuals younger than 45 years of age [19]. The prevalence of oral HPV infection among men and women is approximately 7%, with higher rates correlating the number of reported sexual partners and the number of cigarettes smoked per day [20].

Persistent infection with a high-risk HPV type, particularly type 16, is associated with the development of oropharyngeal and genitourinary cancers. In the USA, where cervical cancer screening is widely available, there are 30,000 new cases of HPV-associated cancer and 6000 HPV-associated cancer deaths each year [3, 21]. Cervical cancer accounts for approximately 30% of those new HPV-related cancer diagnoses and 70% of the deaths [22–24].

**Call Out Box 17.1**

| Oncogenic virus | Associated malignancies |
|---|---|
| Epstein-Barr virus | Burkitt lymphoma, B cell lymphoma, Hodgkin's lymphoma, nasopharyngeal carcinoma |
| Hepatitis B virus | Hepatocellular carcinoma |
| Hepatitis C virus | Hepatocellular carcinoma |
| Human herpesvirus-8 | Kaposi's sarcoma, primary effusion lymphoma |
| Human papillomavirus | Cervical, vulvar, vaginal, penile, anal, oropharyngeal cancers |
| Human T-cell lymphotrophic virus, type 1 | Adult T-cell leukemia |
| Merkel cell polyomavirus | Merkel cell cancer |

## 17.4 Pathogenesis

HPV infection occurs at the site of injury, typically minor abrasions of the skin, mucosal injury that occurs during sexual activity, or trauma related to labor and delivery. It is generally accepted that HPV infection can only be established in the basal epithelial cells [1]. Once HPV enters and infects the basal layer of injured stratified squamous epithelium, a period of latency is followed by active viral replication [25]. Virus-expressed proteins have the potential to alter cellular proliferation and differentiation, resulting in the development of warts and precancerous and cancerous lesions [1].

The incidence of HPV infection is extremely high, so it is fortunate that the vast majority of infections resolve over time. Ninety percent of HPV infections are cleared within 2 years, with a median time to resolution of 9 months [25, 26]. Infections caused by high-risk HPV types that do not clear pose an oncogenic risk (Fig. 17.2).

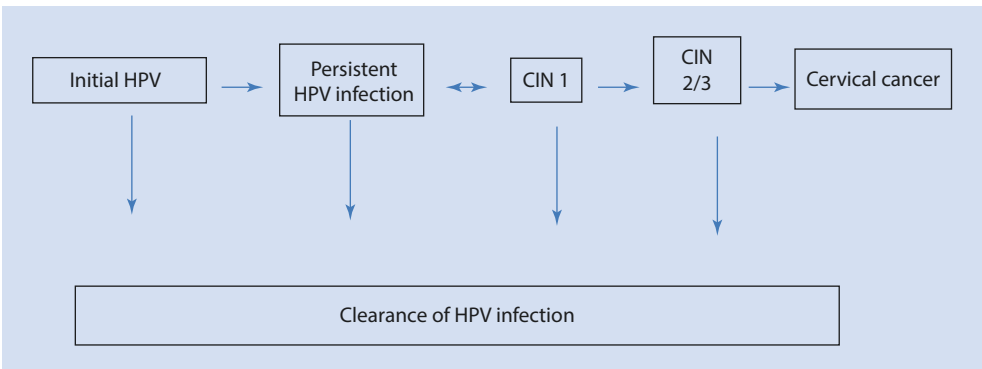


**Fig. 17.2** Natural history of HPV infection. The majority of HPV infections clear spontaneously, even when they are associated with low-grade cervical intraepithelial neoplasia (CIN 1). Advanced CIN (grades 2/3) are less likely to clear spontaneously. Persistent grade 2/3 dysplasia requires definitive treatment to prevent progression to carcinoma in situ and cervical cancer

Persistent infection is associated with nonproductive, low-level genome replication allowing for the ongoing expression of the E6 and E7 viral oncogenes, with disruption of normal cell cycle controls [1, 25].

## 17.5 Clinical Manifestations

Most HPV infections are asymptomatic or subclinical. When symptomatic, infection is cutaneous, mucosal, or related to a rare genetic disorder, epidermodysplasia verruciformis. Mucosal infections are divided into low-risk and high-risk groups as determined by the oncogenic potential of the infecting HPV type.

### 17.5.1 Cutaneous Warts

Cutaneous HPV infection is transmitted by direct contact from person to person or following contact with contaminated surfaces. Cutaneous HPV infection can manifest clinically as verruca vulgaris, verruca plana, or plantar warts. Verruca vulgaris refers to common warts. Clinically they appear as well-demarcated, hyperkeratotic papules with a rough surface, typically on the fingers, back of hands, and periungual regions. Common warts are caused by HPV types 2 and 4, among others. Verruca plana refers to flat warts. Lesions are typically elevated, flat, skin-colored papules with irregular borders found on the face and back of the hands. Flat warts are frequently caused by HPV types 3 and 10. Deep plantar warts are deep, painful, hyper-keratinous lesions most frequently occurring on the weight bearing areas of the feet of adolescents and young adults [27, 28]. Plantar warts are typically caused by HPV types 1, 2, and 4. In the majority of cases, cutaneous HPV infections resolve spontaneously within 2 years.

### 17.5.2 Epidermodysplasia Verruciformis

Epidermodysplasia verruciformis is a rare autosomal recessive disorder associated with an immune deficiency that specifically leads to an increased susceptibility to HPV infections [29]. Patients can present with disseminated verruca plana or with verruca vulgaris covering light-exposed areas during childhood. Over time, the lesions have the potential for malignant transformation into squamous cell carcinomas [27–29].

### 17.5.3 Recurrent Juvenile Respiratory Papillomatosis

Perinatal transmission of HPV type 6 or 11, from mother to child, can result in HPV infection of the infant respiratory tract with the subsequent development of recurrent papillomas along the airway. Infants with respiratory papillomas may present with stridor, respiratory distress, or hoarseness. Recurrent juvenile respiratory papillomas are seen most commonly in the larynx. The lesions can grow fairly quickly, leading to concerns for airway obstruction. Children may require repeated surgical procedures too since effective, curative therapies have remained elusive [30].

### 17.5.4 Anogenital Cutaneous HPV Infection

Most anogenital cutaneous HPV infections are asymptomatic. Infections that become clinically evident manifest as condyloma acuminata, a condition more commonly known as anogenital warts. Ninety percent of anogenital warts are caused by HPV types 6 and 11. They are known to be the most prevalent sexually transmitted infection in the USA and considered to be the most prevalent sexually transmitted infection in the world [9]. The appearance of these lesions can vary from discrete, small papules to larger cauliflower-like masses present in the anogenital area [28]. The lesions have a moist, fleshy feel and are often multifocal.

## 17.6 The Oncogenic Potential of HPV Infection

Each year, more than 30,000 new cases of cancer are attributed to HPV infection in the USA alone. Forty percent of the newly diagnosed HPV-associated malignancies each year are different stages of cervical cancer. Despite the existence of cervical cancer screening programs in the USA, 4000 women die each year from cervical cancer [22–24]. High-risk HPV types are responsible for up to 100% of cervical cancers, 90% of anal cancers, and more than 60% of vaginal, vulvar, penile, and oropharyngeal cancers [3, 9, 28, 31, 32]. By far, the most commonly identified HPV type causing malignancy is HPV type 16.

In areas where rates of cigarette smoking have dropped over the last three decades, the prevalence of smoking-related oropharyngeal cancers has declined dramatically. With that success, the percentage of oropharyngeal cancers attributable to HPV infection rose from 16% in the late 1980s to 73% in the early 2000s [33]. HPV infection now accounts for the majority of newly diagnosed oropharyngeal cancer. Risk factors associated with the development of HPV-associated oropharyngeal cancer in both men and women include oral infection with a high-risk HPV type, smoking, and the total number of lifetime sexual partners [33, 34].

## 17.7 Diagnosis

The diagnosis of cutaneous warts or anogenital warts is made clinically by visualizing the lesions. Subclinical HPV infection may be made presumptively during colposcopy or anoscopy, particularly when acetic acid solution is applied to the mucosa during the procedure (Fig. 17.3). Minor cytologic

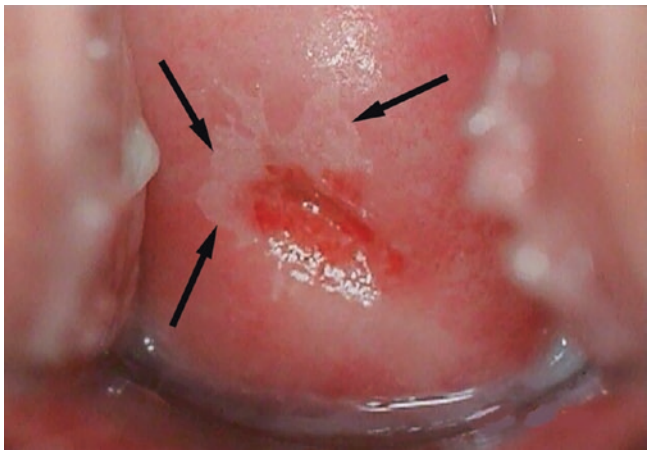

**Fig. 17.3** Shown is a cervix with mild dysplasia as visualized by colposcopy after applying 3% acetic acid solution. The acetic acid clears away mucus allowing a more thorough and detailed examination of any abnormal areas. The acetic acid solution also changes the appearance of the abnormal areas so they become more obvious to the examiner. Abnormal cell layers appear white (*arrows*)

**Fig. 17.4** Shown is a classic image of penile condyloma acuminata. The cauliflower-like lesions are multifocal, nearly circumferential at the corona with smaller lesions noted on the dorsal aspect of the penile shaft. The image was obtained from the US Centers for Disease Control and Prevention, Division of STD Prevention

changes seen on Papanicolau (Pap) smear are nonspecific, but findings consistent with moderate to severe cervical intraepithelial neoplasia certainly implicate HPV. DNA-based testing can be used to confirm the presence of HPV and to classify the infecting type as low or high risk.

Papanicolaou cytology screening involves obtaining cells from the cervix and vagina, including the ecto- and endocervix junction, where precancerous and cancerous lesions tend to develop. The cells are stained and visualized microscopically for dysplastic changes (Fig. 17.4). The technique has variable sensitivity and specificity for the detection of dysplasia and a high rate of interobserver variability. Despite these limitations, Pap smear testing remains the primary method used for cervical cancer screening [26, 34–36].

Pap smear screening can be performed using cells collected from one of two ways. The conventional Pap smear evaluates cervical or vaginal cells obtained by using a brush or spatula to gently scrape cells from the anatomic site. The cells are transferred directly from the brush or spatula onto a glass microscope slide and then preserved using a chemical fixative. In contrast, the newer liquid-based Pap tests evaluate cervical or vaginal cells obtained by a brush or spatula that is placed in a liquid transport medium. The sample is transferred to the laboratory, where it is centrifuged, and the cells plated as thin layers onto a glass slide. While the liquid-based test can be used to detect multiple infections (i.e., HPV, gonorrhea, chlamydia) and allows for improved filtration of blood and debris, it is no more sensitive or specific than conventional Pap testing [37].

Several different diagnostic test types are now commercially available for the detection of high-risk HPV types. DNA-based screening assays detect HPV types 16, 18, and a pool of other high-risk types. Genotyping screening assays, while costly, reveal the specific infecting HPV type. An mRNA-based screening test that detects oncogene E6 and E7 transcripts, while not widely used, is also available [38]. Collectively, high-risk HPV diagnostic testing is designed to overcome the limitations of cytology by providing more sensitive, more specific, and more reproducible results, without substantial interobserver variability in interpretation [26, 39]. Currently, Pap testing remains the standard for cervical cancer screening of women. When high-risk HPV-specific testing is performed, it is done so in conjunction with cytology.

## 17.8 Prevention of HPV Infection and HPV-Related Disease

### 17.8.1 Cervical Cancer Screening

Most cervical cancer can be prevented through the detection and management of precancerous changes in the cervix through Pap screening [4]. Over the last 30 years, routine cytology screening performed in the USA has led to an estimated 50% reduction in the incidence of cervical cancer [37].

Current guidelines recommend cervical cancer screening starting at 21 years of age, independent of reported sexual activity or HPV vaccination status. Cytology alone is performed every 3 years until the age of 30 years. For women between the ages of 30 and 65 years, cytology examinations should continue every 3 years, with or without HPV-specific diagnostic testing every 5 years. Women older than 65 years who have had normal prior Pap screening results and those with no history of cervical intraepithelial neoplasia (CIN) grade 2 or higher no longer need screening [4, 37].

Manifestations of HPV-associated disease can progress quickly and be more severe in individuals with underlying immune deficiencies. As such, human immunodeficiency virus (HIV)-infected women should be screened more frequently than every 3 years for cervical dysplasia. Current guidelines suggest that Pap screening be performed twice

during the first year of the woman's HIV diagnosis and annually thereafter. Women who have had a total hysterectomy, including complete removal of the cervix, no longer need cytology screening or HPV testing [37]. It is important to remember that all adults who have an anatomic cervix remain at risk for developing HPV-associated cervical dysplasia and cervical cancer including those who identify themselves as male gender and those who have had sex reassignment surgery.

## 17.8.2 Active Immunization

### 17.8.2.1 HPV Vaccines

Three formulations of HPV vaccines are currently licensed for the prevention of HPV infection and HPV-associated disease. The bivalent (HPV2) vaccine includes high-risk HPV type 16 and 18 antigens. It was developed specifically as a cervical cancer vaccine, so it was studied and approved for use only in females. It is no longer available in the USA, but it is widely used in many parts of the world. Quadrivalent (HPV4) vaccine includes the same high-risk HPV type 16 and 18 antigens along with low-risk HPV type 6 and 11 antigens. It was developed for the prevention of cervical, anal, vaginal, vulvar, and penile cancers and for the prevention of genital warts. HPV4 was studied and approved for use in both females and males. HPV4 is no longer available commercially because a 9-valent (HPV9) vaccine was subsequently introduced by the same manufacturer. HPV9 includes the same 4 antigens that were used in HPV4 (HPV types 6, 11, 16, and 18), along with antigens for the additional 5 high-risk HPV types 31, 33, 45, 52, and 58. Like HPV4, it is approved and recommended for use in both females and males [▶ Call Out Box 17.2]. At the present time, the only HPV vaccine available for use in the USA is HPV9 [40]. Approved HPV vaccines are preventative, not therapeutic. Vaccination provides no benefit for HPV types already acquired or HPV-associated disease that is already present. Even the 9-valent HPV vaccine does not offer protection from all potentially infecting high-risk HPV types, so cervical cancer screening recommendations remain the same for immunized and unimmunized women.

The US Advisory Committee on Immunization Practices (ACIP) recommends universal HPV vaccination for females starting at age 11 or 12 years, with "catch-up" for those who not yet been vaccinated through age 26 years. Similarly, universal HPV vaccination is recommended for males starting at age 11 or 12 years, with "catch-up" through age 21 in those who have not yet been vaccinated. Females and males can be immunized starting as early as 9 years of age. Vaccination of males who are at higher risk of acquiring HPV infection, including men who have sex with men and HIV-infected men, is recommended through age 26 years [3]. The HPV9 vaccine series is administered as two doses in those who receive the first dose before 15 years of age. The two doses are administered 6 months apart. Individuals who initiate the HPV9 vaccine series at 15 years of age or later should receive three doses of vaccine on a schedule of 0, 1, and 6 months [40]. The rationale for universal HPV vaccination at age 11 or 12 years is based on several important factors. First, HPV vaccine is safe and immunogenic in this age group, with younger adolescents achieving higher antibody titers than older adolescents and young adults. Second, the vaccine is meant to be preventative. At age 12 years, the vast majority of adolescents are not yet sexually active and have therefore not yet been exposed to or infected with HPV. Third, adolescents in the 11–12-year-old age group are already being seen by their providers for other routinely recommended vaccines [17].

More than 90 million doses of HPV vaccine have been distributed in the USA since first licensed in 2006. Safety data show that the most common side effects of the vaccine are mild, including local injection site pain, redness, or swelling. In areas of the world where HPV vaccine coverage rates among females exceeded 50%, infections caused by HPV types 16 and 18 dropped by 68%, and reported cases of anogenital warts among females dropped by 61%. A modest reduction in cases of anogenital warts among males was also reported, likely a result of herd immunity [41]. In countries where HPV vaccine coverage among females was less than 50%, reductions in infections caused by HPV types 16 and 18 were still observed, but there was no impact on anogenital warts in males, suggesting a lack of herd immunity with lower female vaccination rates and emphasizing the importance of maintaining high vaccination rates to achieve the best overall public health benefits [41].

Following the introduction of HPV vaccine into the US population, the prevalence of vaccine-type infection and the incidence of CIN decreased significantly among 13- to 26-year-old and 15- to 19-year-old women, respectively [17, 42, 43]. Despite robust data demonstrating the safety and efficacy of HPV vaccine in cancer prevention, vaccination rates continue to remain suboptimal. The 2015 Teen National Immunization Survey found that, nationally, only 42% and 28% of females and males, respectively, ages 13–17 years had completed their HPV vaccine series [3].

**Call Out Box 17.2**

| HPV vaccine | HPV antigens included |
|---|---|
| Bivalent HPV vaccine | 16, 18 |
| Quadrivalent HPV vaccine | 6, 11, 16, 18 |
| 9-valent HPV vaccine | 6, 11, 16, 18, 31, 33, 45, 52, 58 |

## 17.8.3 HPV Vaccine Acceptance and Vaccine Hesitancy [▶ Call Out Box 17.3]

Adolescent HPV vaccine uptake is influenced by variables throughout the health-care delivery system, including those at the level of the patient, the family, the provider, and the provider's practice. Parental HPV vaccine hesitancy is

**Call Out Box 17.3**

| Factors associated with HPV vaccine acceptance | Factors associated with HPV vaccine hesitancy |
|---|---|
| Perception of disease severity | Lack of provider vaccine recommendation |
| Belief that HPV vaccine prevents cancer | Low perceived disease risk among adolescents |
| Patient is an older adolescent | Vaccine safety concerns |
| Hearing a strong provider vaccine recommendation | Associating HPV vaccine with sexual activity |
| | Concerns for parental refusal |

associated with concerns regarding the need to discuss sex with young adolescents prior to receiving HPV vaccine, the erroneous belief that vaccinating adolescents against HPV condones sexual activity, and a low perception of adolescent disease risk [44–46]. The two factors most consistently associated with parental and patient HPV vaccine acceptance is the belief that HPV vaccine prevents cancer and the receipt of a strong vaccine recommendation from the provider. Parents of adolescents consistently report that providers recommend HPV vaccine with less conviction than they recommend other adolescent vaccines [47–58].

The lack of a strong provider vaccine recommendation is a common reason for adolescent non-vaccination [56, 59]. Weak and inconsistent provider recommendations have been acknowledged by the National Vaccine Advisory Committee as a major obstacle to HPV vaccine completion [60]. Providers report using a risk-based approach to recommending vaccine, failure to recommend same-day vaccination, and not readdressing HPV vaccine during subsequent visits if the series was initially declined or deferred [61, 62]. Providers also report being less likely to recommend HPV vaccine to 11- to 12-year-olds and to boys when compared to 13- to 18-year-olds and to females [61–64]. Specifically, providers who believe that HPV vaccine recommendations need to be associated with a discussion of sexual activity are less likely to recommend the vaccine to their younger adolescents [46, 62, 65]. Physicians who perceive that parents are likely to defer vaccine are similarly less likely to discuss HPV vaccination at the 11–12-year-old visit, despite the fact that physicians overestimate parental vaccine hesitancy [66]. As with parental vaccine acceptance, the one factor that is consistently associated with provider HPV vaccine recommendation is their belief that HPV vaccine is effective in preventing cancer [47–50, 54, 60, 67, 68].

Practice level obstacles to HPV vaccine completion include reduced opportunities for vaccine education and administration due to fewer routine or scheduled medical visits for patients in this age group. Missed opportunities are also quite common. A missed opportunity is defined as medical visit for something other than vaccination, where the need for vaccination is overlooked [62, 65, 69, 70].

A variety of interventions to improve HPV vaccine coverage rates have been studied, including community-wide media information campaigns, education brochures for patients and parents, on-site provider education, and reminder-recall systems [71–76]. Multifaceted approaches that include and engage patients, parents, providers, nurses, administrative office staff, and other members of the practice have the most success in improving vaccine uptake (71). Similarly, interventions designed to bundle HPV vaccine education with other routinely discussed cancer prevention guidance show promise for improved vaccine acceptance [77].

Providers who initiate the vaccine discussion, provide a strong presumptive recommendation, and continue to provide the same consistent recommendation despite real or perceived patient or parental hesitancy increase the likelihood that their patients will be immunized during that medical encounter. The consistent message for a strong provider recommendation can also be effective during a later visit for those who are not vaccinated during an earlier encounter.

**Case Study**

**Practical Example**

*A previously healthy 17-year-old male presents to his pediatrician with penile lesions that has persisted for the past several weeks. The lesions are not pruritic or painful. There has been no discharge from the lesions. He denies fevers, abdominal pain, or dysuria. He reports being sexually active with multiple female partners. He uses condoms "sometimes." On physical examination, there are several flesh-colored, cauliflower-like masses on the shaft of the penis (◘ Fig. 17.4). The pediatrician informs the teen that he has a sexually transmitted infection caused by HPV called condyloma acuminata, a problem more commonly referred to as genital warts. The patient, who is visibly distressed by the news, asks if he can receive the HPV vaccine to treat the genital warts.*

Condyloma acuminate refers specifically to the condition of anogenital warts. It is the most common presentation of symptomatic HPV infection. While HPV vaccination is effective in preventing the acquisition of HPV infection, it is not effective in the treatment of HPV-associated disease. Since individuals can be infected with multiple HPV types during the course of a lifetime, and the current HPV vaccine includes antigens for nine different HPV types, the patient should receive the HPV vaccine series to help prevent related infections in the future. He should also be counseled that his infection is highly contagious, so future sexual activity should involve the use of barrier protection, such as condoms. All patients who are diagnosed with one sexually transmitted infection (STI) should undergo a diagnostic evaluation for the presence of other STIs, including chlamydia, gonorrhea HIV, hepatitis C, and syphilis.

## 17.9 Exercise

Please refer to the supplementary information section for answers to these exercises.

1. Antigens for which of the following HPV types are included in all three HPV vaccines approved for use in the USA (HPV2, HPV4, and HPV9)?
   (a) HPV 6
   (b) HPV 11
   (c) HPV 16
   (d) HPV 3
   (e) HPV 1

2. Which of the following cancers are known to be associated with HPV infection?
   (a) Cervical, oropharyngeal, anal
   (b) Penile, gastric, cervical
   (c) Anal, lung, vulvar
   (d) Vaginal, breast, penile
   (e) Vulvar, anal, colon

3. True or false: HPV9 vaccine is effective in the prevention and treatment of HPV infection.

4. Which of the following statements are true about the administration of HPV9 vaccine to 11 or 12 years? Circle all that may apply
   (a) Younger adolescents have a more robust response to HPV9 vaccine than older adolescents and young adults
   (b) HPV9 vaccine is only effective if administered prior to infection
   (c) Parents of younger adolescents are more likely to accept HPV vaccine than parents of older adolescents
   (d) Administering HPV vaccine at the 11- or 12-year-old visit bundles vaccine with the other adolescent vaccinations, including tetanus and meningococcal vaccines.



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# Prostatitis, Epididymitis, and Orchitis

## Acute Scrotal Pain

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**Learning Objectives**

- Understand the clinical presentation of acute epididymitis, orchitis, and prostatitis.
- Describe the most common pathogens that cause epididymitis, orchitis, and prostatitis.
- Outline the approach used to diagnosis and differentiate between epididymitis, orchitis, and prostatitis.

## 18.1 Introduction to the Problem

### 18.1.1 Definitions

#### Anatomy

The anatomic relationships of the major components of the male reproductive system are shown in Fig. 18.1. Anatomic structures that are identified with labels in Fig. 18.1 and described here in the text are written in **bold font**. The **scrotum** consists of two identical compartments, each containing a **testis**, **epididymis**, and **ductus deferens**. The **testis** is positioned as the most anterior structure in the **scrotum**. Testicular size and shape are often compared to those of a large olive or small plum. In the young adolescent, testicular enlargement to a volume of 4 mL is the first sign of puberty. Testicular growth and maturation ultimately result in adult testes with volumes of 25 mL each. The appendix testis, a small remnant of the embryologic Müllerian duct, is located on the anterior-superior aspect of each **testis**. Spermatozoa, produced in the **testis**, mature in the **epididymis**, a comma-shaped structure positioned directly posterior to the **testis**, with its head overhanging the upper pole of the testicle. The appendix epididymis, a vestigial structure of the embryonic Wolffian duct, is located at the head of the epididymis. The **epididymis** is a tightly coiled tube that connects the testicle to the **ductus deferens**. The **ductus deferens** transports the mature spermatozoa from the **epididymis** to the **urethra**. At its proximal end, just as it exits the urinary **bladder**, the **urethra** is partially surrounded by the **prostate**. The **prostate** is a muscular, walnut-sized gland that together with the paired **seminal vesicles** produces seminal fluid. The **prostate** is positioned inferior to the **bladder** between the **rectum** and the base of the **penis**.

**Acute epididymitis** refers to inflammation of the epididymis that is often, but not always, secondary to infection. If the testis is also inflamed, the term **epididymo-orchitis** is used. **Orchitis** refers to inflammation of the testicle. When orchitis occurs in the absence of epididymitis, a viral infection is the usual trigger. Mumps, a virus best known for causing parotitis, resulting in painful swelling and inflammation of the parotid glands, also has the proclivity to infect the gonads, especially among individuals who develop the infection after puberty. Acute bacterial orchitis, by itself, is quite unusual, but should be included in the differential diagnosis of acute scrotal pain, particularly in patients who appear toxic. A number of different pyogenic bacteria have been reported as causes, including *Staphylococcus aureus*. Acute **prostatitis** refers to inflammation of the prostate gland, usually secondary to a bacterial infection.

### 18.1.2 Basic Concepts

Complaints of scrotal pain, with or without urinary symptoms, should raise concern for epididymitis, epididymo-orchitis, orchitis, or prostatitis. A detailed medical history and careful physical examination are usually sufficient to further narrow the diagnostic possibilities. A provisional clinical diagnosis is confirmed by performing a few basic laboratory tests. **When a male patient presents with a medical history and physical examination findings consistent with epididymitis, epididymo-orchitis or prostatitis, a sexually transmitted infection should always be considered and the appropriate diagnostic evaluation initiated.** Under these circumstances, empiric antibiotic treatment for the most common sexually

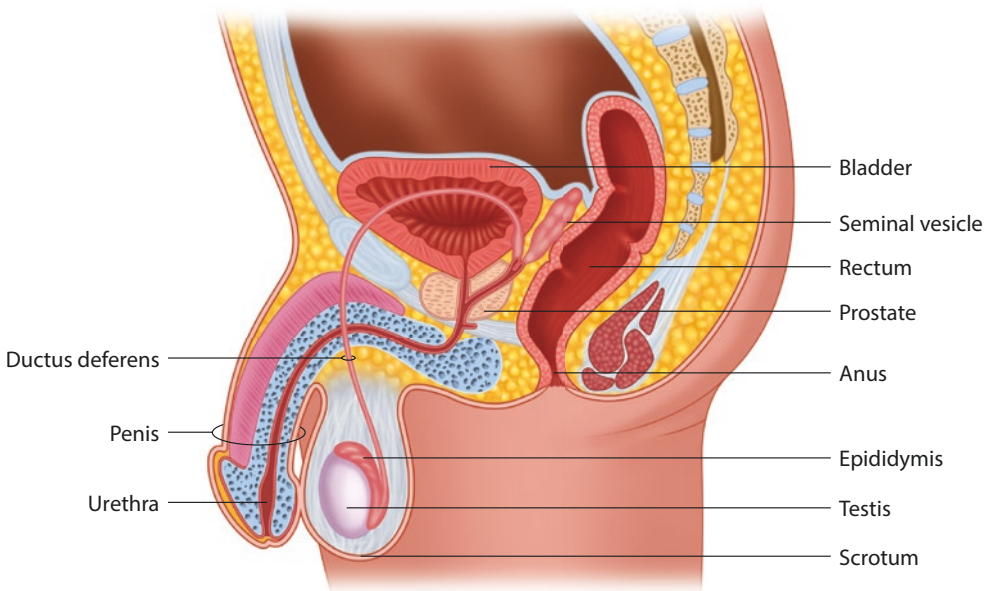


**Fig. 18.1** Drawing of the male reproductive system showing the anatomic relationships of key structures

transmitted etiologies, *Neisseria gonorrhoeae* and *Chlamydia trachomatis*, is almost always warranted even before definitive diagnostic test results become available..

## 18.2 Epididymitis

Epididymitis occurs almost exclusively in sexually active males. The onset of symptoms is abrupt, although not all patients seek medical attention immediately. In some cases, the origin of the pain is vague, although most males will localize the discomfort to the scrotum or its contents. Most infections of the epididymis are unilateral and remain so unless diagnosis and treatment are delayed for an extended period of time. Even when the patient is unable to point out the intrascrotal swelling or tenderness, the findings become obvious during the physical examination. The patient typically has no history of a prior episode. Because the pathogens reach the epididymis in retrograde fashion via the urethra, urethritis with its associated symptoms of pain and burning on urination is a regular finding. The presence of a urethral discharge or pyuria (the presence of leukocytes in the urine when viewed microscopically) in the setting of scrotal pain is an important clue that the underlying clinical diagnosis is likely to be epididymitis. Bacterial urethritis can be associated with impressive pain and burning during urination, but the urethral inflammation associated with chlamydia or gonorrhea infection can also be completely asymptomatic.

During the physical examination of the scrotal contents of a male with bacterial epididymitis, the epididymis on the affected side will be swollen and tender. To identify the epididymis, locate the ductus deferens inside the scrotum and follow it, by palpation, superiorly and posteriorly in the direction of the testis (Fig. 18.1). An infected epididymis is indurated, swollen, and exquisitely painful to even light palpation. Pain relief comes when the scrotum and its contents are elevated. A reactive hydrocele may be present on the side of the infection, but is easily obscured by an intense inflammatory reaction.

Recent genitourinary surgery and existing underlying genitourinary abnormalities are known risk factors for the development of epididymitis unrelated to sexual activity. In these circumstances, the microbiologic cause of the infection is most typically a Gram-negative bacillus that normally colonizes the gastrointestinal tract such as *Escherichia coli* or a *Klebsiella* species. Less commonly, *Pseudomonas* species gain entry and cause infection, especially among patients who have required treatment with multiple courses of antibiotics. *Pseudomonas* species are intrinsically resistant to the more commonly prescribed narrow spectrum antibiotics, giving it a survival advantage in patients treated with those medications. Once the patient becomes colonized with a *Pseudomonas* species, those bacteria can make the same retrograde journey to the epididymis that the intestinal coliform bacteria do.

Epididymitis rarely occurs in prepubertal boys, but when it is seen, diagnostic testing for infection secondary to *Neisseria gonorrhoeae* and *C. trachomatis* should be included in the laboratory assessment. In this age group, the detection of either of these sexually transmitted pathogens must trigger a comprehensive child sexual abuse evaluation.

*C. trachomatis* and *N. gonorrhoeae* are the most common pathogens known to cause epididymitis. Among males and transgender females who report the practice of insertive anal intercourse, enteric Gram-negative bacilli such as *E. coli* also merit consideration as a cause of epididymitis especially when test results for the two common sexually transmitted agents fail to reveal the culprit. A wide variety of other pathogens have been reported to cause epididymitis including other enteric and non-enteric bacteria, *Mycobacterium tuberculosis*, mycobacteria other than tuberculosis, various fungi, viruses, and parasites (Table 18.1). Unusual causes are often discovered unintentionally when routine laboratory testing for common causes reveals an unexpected finding. If, however, the detailed medical history or an underlying chronic medical condition reveals risk factors for infection with a particular organism and the usual agents that cause epididymitis have already been ruled out, a more extensive laboratory investigation is warranted. Moreover, astute clinicians should remain mindful that noninfectious causes of acute scrotal pain may also require investigation. Some of the more important noninfectious causes of acute pain localized to the scrotum include testicular torsion, autoimmune disease, accidental trauma, and trauma inflicted through physical or sexual abuse.

Pain secondary to intrascrotal pathology is not always easily localized to the scrotum. The perceived location of the pain may be nonspecific, or it may be referred to the abdomen. When severe, referred pain that arises from scrotal pathology can mimic an acute abdomen or even appear to localize to the right lower abdominal quadrant raising concerns for acute appendicitis. Testicular torsion should always be considered as a potential cause of acute severe scrotal pain because torsion impairs blood supply to the testis, and without emergency surgical correction, viability of the testis is in jeopardy. Testicular torsion, like acute epididymitis, presents abruptly. The affected testicle may be positioned higher in the scrotum than expected. Urethral symptoms are absent, there is loss of the cremasteric reflex, and Prehn's sign is negative. Stroking the inner thigh and observing a rise of the ipsilateral testicle inside the scrotum is used to demonstrate an intact cremasteric reflex. Prehn's sign is negative if physical elevation of the testicles fails to relieve the scrotal pain. Like the testicle itself, the appendix testis or appendix epididymis can also undergo a torsion event, adding to the differential diagnosis of acute scrotal pain.

Torsion and epididymitis can be difficult to distinguish from one another on clinical grounds. If suspicion for testicular torsion is high, a surgeon with pediatric urologic expertise should be consulted immediately. Ultrasonography of the scrotum, using color Doppler to detect blood flow, should be performed when available any time the clinical findings are equivocal for torsion. Color Doppler ultrasonography easily differentiates between testicular torsion, torsion of the appendix testis or appendix epididymis, and epididymitis. Prior to widespread availability of color Doppler ultrasonography, nuclear medicine scintigraphy was the mainstay imaging technique used to differentiate between torsion events and epididymitis.

**Table 18.1** Etiologic agents of epididymitis, orchitis, and prostatitis

| Epididymitis and epididymo-orchitis | Orchitis without epididymitis | Prostatitis |
|---|---|---|
| Bacteria<br>***Chlamydia trachomatis***<br>***Neisseria gonorrhoeae***<br>*Pseudomonas species*<br>*Escherichia coli* and related coliform bacteria<br>*Mycoplasma* species<br>*Ureaplasma* species<br>*Streptococcus pneumoniae*<br>*Streptococcus equisimilis*<br>*Brucella* species<br>*N. meningitidis*<br>*Treponema pallidum*<br>*Nocardia* species<br>*Tropheryma whipplei*<br>*Haemophilus influenzae*<br>*Salmonella* species<br>*Plesiomonas shigelloides*<br>*Listeria monocytogenes*<br>*Mycobacterium tuberculosis*<br>*Mycobacterium leprae*<br>*Mycobacterium other than tuberculosis and leprae*<br>Viruses<br>Enteroviruses<br>Adenoviruses<br>Cytomegalovirus<br>Fungi<br>*Blastomyces dermatitidis*<br>*Histoplasma capsulatum*<br>*Cryptococcus neoformans*<br>*Coccidioides immitis*<br>*Candida* species<br>Parasites<br>*Trichomonas vaginalis*<br>*Schistosoma* species<br>*Spirometra* species<br>*Wuchereria bancrofti* | Viruses<br>**Mumps**<br>Rubella<br>Enteroviruses<br>Coxsackie viruses<br>Echoviruses<br>Parvovirus B19<br>Lymphocytic choriomeningitis virus<br>Bacteria<br>*Brucella* species<br>*Mycobacterium tuberculosis* | ***Bacteria***<br>***E. coli*** and related coliform bacteria<br>*Chlamydia trachomatis*<br>*Neisseria gonorrhoeae*<br>*Klebsiella pneumoniae*<br>*Proteus mirabilis*<br>*Pseudomonas aeruginosa*<br>*Enterococcus* species<br>Parasites<br>*Trichomonas vaginalis* |

Most common causes are in **bold**

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Table 18.2 shows the similarities and differences between bacterial epididymitis, testicular torsion, and torsion of the testicular appendix.

### 18.2.1 Laboratory Testing

Diagnostic laboratory testing for suspected epididymitis should always include a urinalysis, urine culture, and urine nucleic acid amplification tests (NAAT) for *C. trachomatis* and *N. gonorrhoeae*. Additional testing to evaluate for the presence of other sexually transmitted infections, including HIV, syphilis, hepatitis B, hepatitis C, and trichomoniasis is prudent for patients who are sexually active, especially those previously diagnosed with another sexually transmitted infection. A Gram stain can be performed on urethral secretions collected from patients who describe pain or burning on urination and from those with a urethral discharge. The presence of any Gram-negative intracellular diplococci is diagnostic for gonococcal urethritis. Urethritis can be diagnosed clinically in the presence of a mucoid, mucopurulent, or purulent urethral discharge, or based on laboratory findings from the centrifuged sediment of a first morning voided urine sample. Findings that support a laboratory diagnosis of urethritis include the detection of leukocyte esterase in the urine or microscopic evidence of ten or more leukocytes per high-power field in the centrifuged urine sediment.

**Table 18.2** Similarities and differences between bacterial epididymitis, testicular torsion, and torsion of the testicular appendix

| | Epididymitis | Testicular torsion | Torsion of the testicular appendix |
|---|---|---|---|
| Most common presenting age[a] | Sexually active adolescents and young adult males | Bimodal: Neonates and during puberty | Prepubertal boys |
| Onset | Indolent | Abrupt | Subacute |
| Primary symptoms | Scrotal pain | Scrotal and inguinal pain | Scrotal pain |
| Associated symptoms | Dysuria, urinary frequency, urethral discharge, fevers | Nausea, vomiting, abdominal pain | Typically absent |
| Findings on physical examination | Pain or discomfort localized to the epididymis with overlying scrotal erythema and swelling | Severe pain localized to the affected testicle, with overlying scrotal erythema and swelling. Affected testicle may be elevated in the scrotal sac | Pain or discomfort localized to a mass at the superior or inferior pole of the testicle, little or no testicular tenderness, "blue dot" sign[b] |
| Cremasteric reflex[c] | Present | Absent | Present |
| Prehn's sign | Positive | Negative | Not applicable |
| Color Doppler ultrasonographic findings[d] | Increased blood flow to infected epididymis | Decreased testicular blood flow and/or twisted spermatic cord | Normal testicular perfusion. Variable increase in blood flow on the affected side |
| Management | Antibiotics[e] | Surgical intervention | Supportive, pain management, bed rest<br>Surgery if pain persists |

[a]Majority of cases, but can be seen at all ages
[b]Tender blue nodule located to the upper scrotum
[c]Absence of the cremasteric reflex in boys 6 months or younger may be a normal finding
[d]The utility of color Doppler ultrasonography is variable for evaluating possible torsion among prepubertal boys due to normal lower blood flow to quiescent testes
[e]See the text for the principles of antibiotic management, including microbiologic targets, the critical importance of partner treatment, and the recommendation to refrain from sexual activity for a period of 7 days

### 18.2.2 Treatment Considerations

Presumptive antibiotic therapy should be prescribed for all patients with a clinical diagnosis of epididymitis even before confirmatory test results are available. Antibiotics known to be effective for the treatment of both chlamydia and gonorrhea are needed since the infections are clinically indistinguishable from one another, and coinfection is common. Current treatment regimens recommended by the US Centers for Disease Control and Prevention (CDC) can be found at ► https://www.cdc.gov/std. These recommendations are updated frequently based on epidemiologic data and documented patterns of antimicrobial resistance. Of note, the current recommended length of therapy for the treatment of epididymitis is longer than that recommended for isolated urethritis. Patients who remain symptomatic 72 h after starting empiric antibiotic therapy should be reevaluated. Complications of epididymitis such as abscess formation, testicular infarction, and infertility are rare, but serious.

Patients who are undergoing treatment for epididymitis should abstain from sexual intercourse until 7 days after they and all of their partners have been treated and are asymptomatic. The importance of consistent condom use should be emphasized. Where allowed by law, expedited partner therapy (EPT) should be offered to any partners who are unwilling or unable to be examined and treated directly. When EPT is prescribed, the importance of partner evaluation and treatment should still be discussed. The CDC recommends that patients with chlamydia or gonorrhea infection return for reevaluation and repeat testing 3 months following the initial infection. Reinfection is a regular occurrence due to reexposure within sexual networks, failed or incomplete treatment of sexual partner(s), and/or suboptimal adherence to prescribed treatment regimens.

## 18.3 Orchitis

Orchitis is rarely found in the absence of epididymitis and, like epididymitis, is not typically seen in males who have not yet gone through puberty. The term epididymo-orchitis is used to describe an infection that has extended from the epididymitis to involve the ipsilateral testicle. The pathophysiology of epididymo-orchitis is identical to that already described for epi-

didymitis with the exception that the infection has now progressed retrograde from the urethra, along the length of the epididymis, and has entered the parenchyma of the testicle. Symptoms of epididymo-orchitis include scrotal swelling and testicular pain. Chills and rectal pain may also be present. On physical examination, the overlying scrotal skin may appear shiny and erythematous. Epididymo-orchitis may cause infertility secondary to testicular damage from the infection.

In the absence of epididymitis, isolated orchitis is not usually a sexually transmitted bacterial infection, but instead caused by a virus. Typically both testes are infected via the hematogenous route during a period of viremia. The classic agent of viral orchitis is the mumps virus. As many as 10% of postpubertal males with mumps infection will develop testicular inflammation, often involving both testicles. Parotitis, the classic finding during childhood mumps infection, is also typically present in those who develop orchitis. A male who develops orchitis without obvious, associated epididymitis should be tested for mumps infection regardless of vaccination status. Urine and swabs collected from the opening of Stenson's duct can be sent for viral culture to look for mumps. Where available, the same samples can be tested using a nucleic acid amplification test. Mumps serologies to test for the presence of mumps-specific IgM and IgG during the acute illness, and again later during convalescence, should also be obtained, but interpretation of the results can be difficult. Less common causes of viral orchitis include rubella virus, enteroviruses, coxsackie viruses, echoviruses, Epstein-Barr virus, varicella virus, parvovirus B19, and lymphocytic choriomeningitis virus. Rare reports of non-sexually transmitted bacterial orchitis have included several unusual agents such as *Brucella species* and *Mycobacterium tuberculosis* (Table 18.1).

Noninfectious causes of testicular swelling that should be considered when developing a robust differential diagnosis include testicular cancer, testicular leukemia, Henoch-Schönlein purpura, extraintestinal Crohn's disease, accidental trauma, and trauma inflicted during physical or sexual abuse.

## 18.4 Prostatitis

Known risk factors for acute bacterial prostatitis include recent urinary tract infection, a recent urologic procedure, and insertive anal intercourse. The infection is also more common among males who have sex with males. Acute bacterial prostatitis occurs when bacteria migrate from the urethra in retrograde fashion to the prostatic urethra and into the parenchyma of the prostate gland. Onset of the illness is abrupt and includes systemic symptoms such as fever, chills, nausea, and vomiting. Signs and symptoms that may help to localize the source of the problem to the prostate include pain or burning on urination, urinary frequency, incontinence, dribbling, urgency, hesitancy, or retention. Urine may appear cloudy. Other symptoms can include complaints of back, pelvic or perineal pain, pain in the external genitalia, testicular aching, and pain with ejaculation. On rectal examination, the prostate is enlarged, boggy, and sore when palpated. *E. coli* is the most common bacterial cause of acute prostatitis. Other causes include the sexually transmitted pathogens *C. trachomatis*, *N. gonorrhoeae*, *and Trichomonas vaginalis*. *Enterococcus species*, *Klebsiella pneumoniae, Proteus mirabilis,* and *Pseudomonas aeruginosa* may also infect the prostate (Table 18.1). Antimicrobial treatment is directed against the known or suspected underlying cause. Improvement of symptoms can be slow and gradual even when appropriate antimicrobial therapy is prescribed.

**Case Study**

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**Practical Examples**

1. A 17-year-old boy developed complaints of penile discharge for the past week. Over the last 2 days, he began to notice pain localized to the right side of his scrotum. He describes having three different male sexual partners over the last 2 months. Each time, sexual activity included mutual oral sex and insertive anal intercourse. On physical examination, a purulent urethral discharge was noted. Palpation of the scrotal contents revealed tenderness of the epididymis on the right side. The patient's pain improved significantly when the scrotum was elevated indicating a positive Prehn's sign. Laboratory testing included a Gram stain of the urethral discharge, urine NAAT for gonorrhea and chlamydia, and a throat swab for gonorrhea NAAT. The Gram stain of the urethral discharge showed large numbers of polymorphonuclear leukocytes per high-power field and intracellular Gram-negative diplococci. The patient was diagnosed with gonorrheal urethritis and epididymitis. He was treated with a single parenteral dose of ceftriaxone and a 10-day course of oral doxycycline in accordance with CDC treatment guidelines. He was instructed to return for additional medical care if his symptoms continued for more than 3 days. Patient counseling included a discussion of the importance of consistent condom use, the importance of partner therapy, a recommendation for 7 days of abstinence after all partners and self are treated, and the need for repeat testing to evaluate for possible reinfection in 3 months' time. The patient was also made aware that a preexposure prophylaxis program for the prevention of HIV infection was available. Two days later, the patient's urine NAAT for gonorrhea was reported to be positive. The patient was contacted by telephone to convey the results. His symptoms had resolved almost completely. The antibiotics administered empirically while awaiting those results had already treated his gonorrhea infection. Expedited partner therapy had already been addressed, and the necessary counseling topics discussed.

His follow-up appointment was on the calendar for retesting in 3 months' time.

2. A 26-year-old man presented for medical attention because of a 1-day history of progressive pain on the left side of his scrotum. He had no dysuria, frequency, or urgency. He recently became sexually active with one female partner who has remained symptom-free. On physical examination, the man had left-sided scrotal tenderness. There was no penile discharge. A color Doppler ultrasound was performed urgently to evaluate for a possible torsion event. No evidence of torsion was identified. Ultrasonographic findings were consistent with a diagnosis of epididymitis. Additional diagnostic testing was initiated, including HIV and syphilis testing and urine NAAT for gonorrhea and chlamydia. The patient was treated empirically for epididymitis presumed to be caused by chlamydia and gonorrhea. Expedited partner therapy, legal in his state of residence, was offered and prescribed. The man was advised that his partner should seek medical evaluation and that they should abstain from sexual activity for 7 days after treatment. He was asked to return to the office to evaluate for possible reinfection in 3 months' time. The importance of consistent condom use was stressed. One day later, results of the urine NAAT became available indicating that he had been infected with chlamydia. The patient was contacted to review the diagnostic test results, although both he and his partner had already been treated with appropriate antibiotics, and follow-up had already been arranged.

## 18.5 Exercises

Please refer to the supplementary information section for answers to these exercises.

1. A 24-year-old male complains of unilateral scrotal pain and cloudy urine for the last 3 days. He has no systemic symptoms. He has been sexually active with two female partners. On examination, he has a tender, indurated epididymis, a positive Prehn's sign, and normal cremasteric reflex. What is the MOST likely diagnosis?
   a. Testicular torsion
   b. Epididymitis
   c. Orchitis
   d. Prostatitis

2. In the case described above, which of the following should be done next? (select all that apply)
   a. Urine Gram stain, urinalysis, urine culture, and nucleic acid amplification testing for gonorrhea and chlamydia
   b. Presumptive treatment with antibiotics
   c. HIV testing
   d. Urinalysis and urine culture only
   e. A, B, and C

3. An 18-year-old transgender female presents with acute onset of fever, chills, and body aches. She describes dysuria, a clear urethral discharge, difficulty initiating her urine stream, and pain in her perineum and rectum. She is sexually active with multiple male partners, including mutual oral sex and insertive anal intercourse. She has no history of genital surgery. Her clinical presentation is most consistent with:
   a. Torsed testicle
   b. Prostatitis
   c. Ovarian torsion
   d. Influenza infection
   e. Mumps

## 18.6 Summary

Acute scrotal pain has many potential causes, including several important infectious diseases. Epididymitis occurs regularly among sexually active adolescents and young adults and is usually caused by *N. gonorrhoeae* and *C. trachomatis* following sexual transmission. The copresence of symptomatic or asymptomatic urethritis is expected. Epididymitis can be difficult to distinguish clinically from testicular torsion. Scrotal ultrasonography with color Doppler, together with an urgent surgical consultation, should be obtained if testicular torsion is being considered. Orchitis, most commonly seen with concomitant epididymitis, is also typically caused by *N. gonorrhoeae* and *C. trachomatis* following sexual transmission. When orchitis is present without epididymitis, a viral etiology of the infection is probable. The most classic and best-described cause of viral orchitis is mumps. Acute bacterial prostatitis presents as a systemic illness with urinary complaints, perineal pain, and painful ejaculation. Risk factors for the development of bacterial prostatitis include urinary tract infection, urinary retention, and recent urologic surgery. Males who have sex with males are also at higher risk for development acute bacterial infections of the prostate.

## Further Reading

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### Related links to frequently used references

Extended partner therapy (EPT guidelines): CDC: https://www.cdc.gov/std/ept/.

Guttmacher Institute: https://www.guttmacher.org/state-policy/explore/partner-treatment-stis.

Sexually transmitted diseases treatment guidelines: https://www.cdc.gov/std/tg2015/tg-2015-print.pdf.

# Vaginitis, Mucopurulent Cervicitis, and Pelvic Inflammatory Disease

## Vaginal Discharge

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**Learning Objectives**

- Formulate a differential diagnosis for a female presenting with vaginal discharge.
- Identify appropriate diagnostic tools, including point-of-care tests and laboratory tests, to determine the etiology of vaginal discharge
- Identify the preferred treatment regimens for the common causes of vaginal discharge
- Describe appropriate screening recommendations for sexually transmitted infections in adolescent and young adult females
- Describe recommended STI preventative measures
- Describe appropriate management for a sexual partner exposed to an STI

## 19.1 Definitions

**Physiologic leukorrhea** - A thin, white or yellowish, odorless vaginal discharge. This benign condition is caused by vaginal mucous production. The discharge is comprised of mucous, sloughed vaginal epithelial cells, and normal vaginal flora. It is the most common cause of vaginal discharge.

**Dyspareunia** - Difficult or painful penetrative intercourse.

**Friable cervix** - An inflamed cervix that is easily irritated and is prone to bleeding.

**Pelvic inflammatory disease (PID)** - An acute ascending inflammatory and infectious condition of the upper reproductive tract in females, involving the uterus, fallopian tubes, or ovaries, with possible involvement of neighboring organs.

**Fitz**-Hugh-Curtis syndrome - An ascending sequelae of an STI with perihepatitis and inflammation of the liver capsule.

**Mucopurulent cervicitis (MPC)** - The presence of mucopurulent discharge from the cervical os and cervical friability on physical examination, frequently associated with infections caused by *Chlamydia trachomatis* and *Neisseria gonorrhoeae*.

**Nucleic acid amplification test (NAAT)** - Highly sensitive diagnostic tests used to amplify pathogen-specific nucleic acid sequences from biological samples such as urine. NAAT tests are the recommended diagnostic tools used to identify the presence of *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, and *Trichomonas vaginalis* genitourinary infections.

**Expedited partner therapy (EPT)** - The practice of prescribing antibiotic treatment to sexual partners of patients diagnosed with an STI without a formal patient encounter with them.

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## 19.2 Introduction to the Problem

Vaginal discharge is an extremely common complaint that is associated with a variety of causes [1] [▶ Call Out Box 19.1]. Its presence can be alarming because of the concern that its presence may be secondary to a sexually transmitted infection (STI) such as *Chlamydia trachomatis* or *Neisseria gonorrhoeae*. Adolescent females presenting with vaginal discharge should undergo STI testing since nearly half of the 20 million new STIs diagnosed in the United States each year occur among 15–24-year-olds (◘ Fig. 19.1) [2]. Behavioral, developmental, societal, and anatomic factors that contribute to the high prevalence of STIs among adolescent and young adult females are shown in ▶ Call Out Box 19.2. There are also disparities in rates of reported STIs among different racial and ethnic minority groups. In the United States, for example, the prevalence of chlamydia and gonorrhea among Black, American Indian, Alaskan Native, and Hispanic women are significantly higher than among White women [3]. Disproportional STI rates also correlate with other fundamental social determinants of health status such as poverty, income inequality, unemployment, low educational attainment, lack of transportation, lack of health insurance, and reduced access to health care [4].

The majority of female STIs do not present with vaginal discharge. Infected patients are frequently asymptomatic and may, therefore, unknowingly transmit those STIs to their sexual partners. Strategic approaches designed to decrease rates of STI transmission and to prevent their clinical sequelae demand rapid detection and treatment of asymptomatic and symptomatic infections alike. Current guidelines recommend that all females under 25 years of age be screened annually for chlamydia and gonorrhea to detect asymptomatic infections. Symptomatic females should be tested at the time they seek care for a new vaginal discharge or related symptom.

Although STIs are extremely common, the presence of a vaginal discharge is more commonly attributed to a noninfectious cause. For example, physiologic leukorrhea, a benign condition of mucous production, is present in almost all females. The discharge, comprised of mucous, epithelial cells, and bacteria normally present in the vagina, is thin, white, and lacking foul odor. Adolescent females should be reassured that physiologic leukorrhea is normal and does not require any intervention. A change in the quality of the discharge should trigger the provider to consider performing diagnostic testing for another cause. **Consider the case presentation and associated questions in** ▶ Call Out Box 19.3.

**Call Out Box 19.1**

***Differential Diagnosis of Vaginal Discharge***

**Infectious Etiologies**

- Bacterial vaginosis
- *Trichomonas vaginalis*
- Vulvovaginal candidiasis
- *Chlamydia trachomatis*
- *Neisseria gonorrhoeae*
- Uncommon beyond young childhood: *Streptococcus pyogenes*
- Uncommon: *Shigella* species
- Uncommon cause of vaginitis with intense itching, preschool age: *Enterobius vermicularis*

**Noninfectious Etiologies**

- Physiologic leukorrhea
- Chemical irritation from exposure to fragranced soap, perfume, douche, or bubble bath
- Physical irritation from trauma or an intrauterine device
- Allergic reaction to latex condoms, lubricant, or topical medication
- Use of oral contraceptives
- Retained foreign body

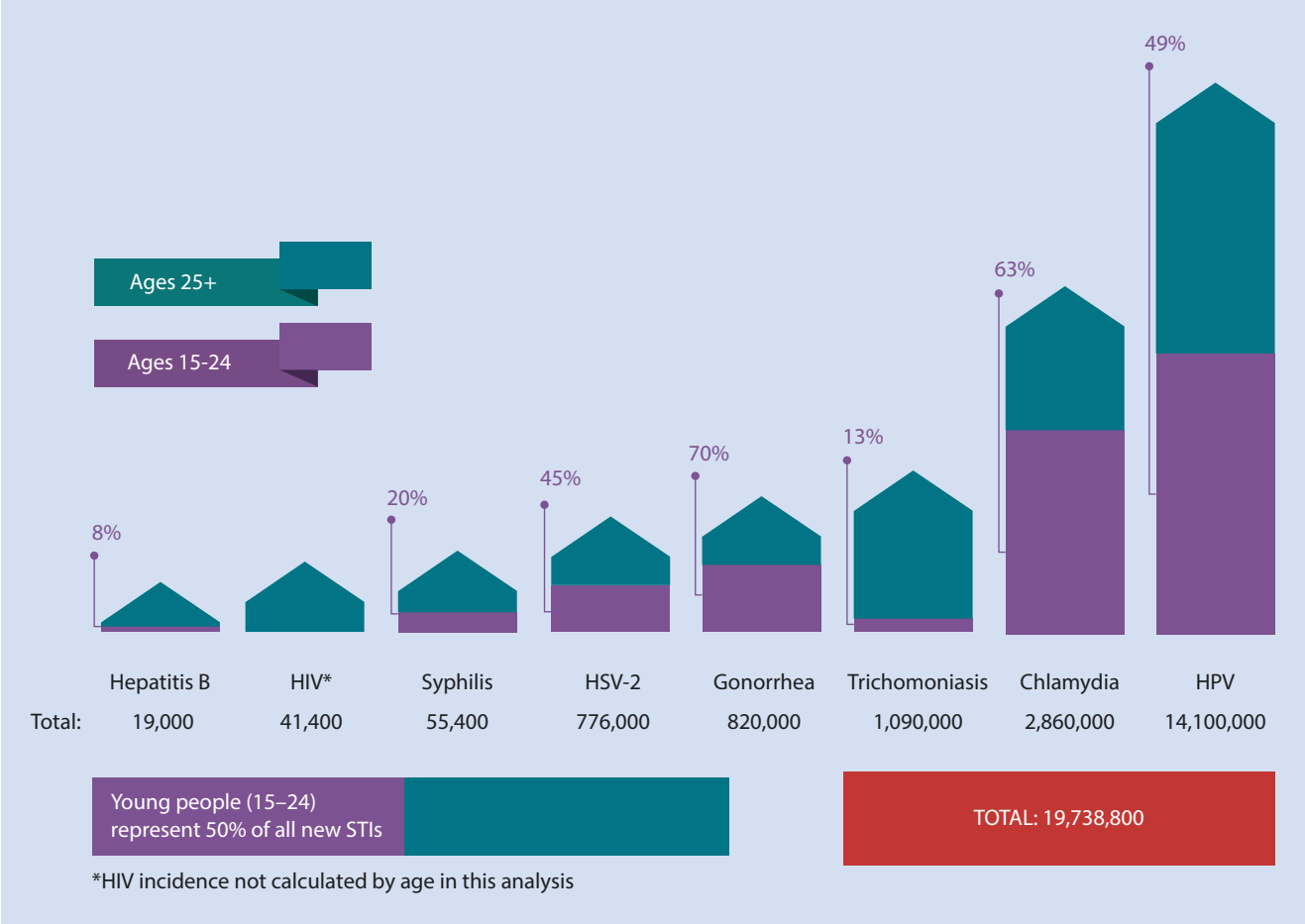



**Fig. 19.1** Estimated number of new STIs in the United States in 2008. Note 50% of new infections were diagnosed in 15–24-year-olds. (► http://www.cdc.gov/std/stats/STI-Estimates-Fact-Sheet-Feb-2013.pdf)

### Call Out Box 19.2

**Factors Contributing to the High Prevalence of STIs Among Adolescents**

| Behavioral | Developmental | Societal | Anatomic |
|---|---|---|---|
| Multiple short-term, consecutive, and/or overlapping relationships | Feeling invincible to consequences of risky behaviors | Lack of confidentiality when seeking medical care as a minor | The adolescent cervix is lined by columnar epithelium which may be more susceptible to infection compared to the squamous epithelium of the adult cervix |
| Inconsistent condom use | Underdeveloped abstract thinking | Insufficient appropriate sexual education | |
| | Lacking skills to be prepared | | |

### Call Out Box 19.3

A 15-year-old girl presents to her primary care provider with a complaint of vaginal discharge. She reports that she typically has a small amount of clear, odorless discharge, but for the past week she has noticed an increase in an odorless, yellow-green discharge. She denies vaginal itching, burning, or dysuria. She usually has normal monthly menses with her last menses occurring 2 weeks ago. She states that she experienced vaginal bleeding for the first time during intercourse 3 days ago. On review of systems, she denies fever, abdominal pain, nausea, vomiting, or diarrhea. She denies use of any scented soap or perfume in the genital region or douching. When asked about her sexual history, she states that her initial sexual encounter was 1 year ago. She has had three lifetime male partners and only one partner during the last 2 months (her 18-year-old boyfriend). She uses condoms most of the time and has never been on contraception; she has never been pregnant and has never had a sexually transmitted infection (though she does not know if she has ever been tested). She does not know if her boyfriend has had a prior STI but does not think that he has any symptoms of urethral discharge or testicular pain. A speculum examination reveals a thick mucopurulent discharge exuding from the cervical os. After lightly touching the cervix with a cotton swab, some bleeding occurs. There is no vulvar or vaginal inflammation.

- What are the likely causes of the patient's vaginal discharge?
- What is the optimal approach to diagnose her condition?
- What treatment should she receive?
- Are there treatment implications for her partner?

## 19.3 Basic Concepts

### 19.3.1 Evaluation

Providers should use a systematic approach comprised of a comprehensive medical history with a detailed sexual history ▶ Call Out Box 19.4, detailed physical examination, and, when indicated, laboratory testing to determine the etiology of a patient's vaginal discharge. Assessment should begin with a detailed description of the discharge including its color, quantity, and consistency, the presence or absence of an odor, how long the discharge has been present, and whether symptoms occur daily or intermittently. Further questioning should delineate the presence or absence of associated signs and symptoms such as vaginal itching or burning, abdominal or pelvic pain, fever, dyspareunia (pain with intercourse), diarrhea, rash, genital lesions, or urinary complaints including dysuria, urgency, frequency, or hesitancy. Additional history should question the possible use of irritating products in the genital area such as scented soap, bubble bath, perfume, fragranced sanitary pads, douche, or feminine washes. Providers should ask about recent use of oral antibiotics, contraceptives, or topical antifungal creams, either prior to discharge onset or as an attempt to self-treat the discharge. A menstrual history including typical menstrual cycle length, date of last menstrual period, and presence of irregular vaginal bleeding or bleeding after intercourse should be documented. The past medical history should also be considered since chronic systemic medical conditions or medication use may be associated with vaginal infections or inflammation. For example, poorly controlled diabetes mellitus, immunocompromised states, and recent antibiotic use are known risk factors for the development of vulvovaginal candidiasis (vaginal yeast infection). A detailed sexual history should include the number and gender of sexual partners during the past 2 months and lifetime, prior history of any STI, recent exposure to a partner with a known STI, and consistency of condom and contraception use [5].

**Call Out Box 19.4**

**Obtaining a Comprehensive Sexual History [5]**

History should be obtained without judgment and without making assumptions.

History is usually obtained without a parent or guardian present in the room. Provider should reinforce confidentiality prior to asking questions.

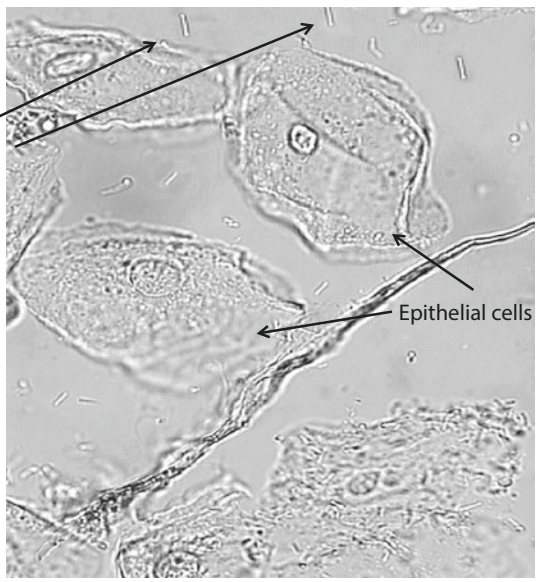
The following should be discussed when obtaining a sexual history:

- Age of sexual debut
- Number and gender of partners: Lifetime and in past 2 months
- Type of sexual activity: Receptive or insertive, oral, vaginal and/or anal sex
- Use of contraception including consistency of condoms or hormonal contraception
- History of any sexually transmitted infections
- Known exposure to any sexually transmitted infections
- History of pregnancy

After determining the medical history, an appropriate physical examination is performed. For most adolescent females presenting with discharge, a pelvic examination is necessary. Treatment of patient-reported symptoms beyond those typical for physiologic leukorrhea is unreliable [6]. While a pelvic examination should always be considered when a female complains of vaginal discharge, it may not be necessary in all cases. For example, a young adolescent female with typical symptoms of physiologic leukorrhea (colorless, odorless, thin discharge with no associated symptoms) who has never been sexually active may not require a pelvic examination.

The pelvic examination should begin with careful inspection of the external genitalia to identify lesions, edema, erythema, or rash on the skin or vulvar mucosa. Next, an internal or speculum exam is performed. Providers should note the presence of any discharge in the vaginal vault along with its color, consistency, quantity, and odor. Next the cervix is observed for signs of inflammation such as erythema, discharge from the cervical os, and the presence of cervical lesions or friability. A bimanual examination is used to assess for the presence of cervical motion tenderness, adnexal tenderness, or uterine tenderness that could indicate the presence of pelvic inflammatory disease (PID), a sequela of an ascending STI.

Diagnostic testing performed during the pelvic examination begins with a wet mount slide of the vaginal discharge. The test is quick, easy, and low cost. The **wet mount slide** is created by using a cotton swab to place a sample of the discharge on a glass microscope slide combined with a few drops of saline. Normal microscopic findings on a wet mount include the presence of *Lactobacilli*, epithelial cells (◘ Fig. 19.2), and a small number of white blood cells (5–10 white blood cells per high-power field is considered normal). Pathologic findings that may be seen on a wet mount include the presence of increased numbers of white blood cells, pseudohyphae, bud-




◘ **Fig. 19.2** Normal wet mount microscopy demonstrating epithelial cells and lactobacilli. (University of Washington STD Prevention Training Center)

ding yeast, trichomonads, or clue cells. On a second glass microscope slide, a sample of the discharge is combined with a few drops of 10% potassium hydroxide. The presence of a fishy, amine odor either before or after the potassium hydroxide is added is termed a positive **whiff test** and is consistent with the presence of bacterial vaginosis or trichomoniasis. In addition, the potassium hydroxide breaks down epithelial cells facilitating the visualization of any budding yeast or pseudohyphae that are present in vulvovaginal candidiasis. Testing the pH of the discharge using narrow range pH paper also plays a diagnostic role. Physiologic discharge typically has a pH less than 4.5. The presence of bacterial vaginosis or trichomoniasis are typically associated with a vaginal pH higher than 4.5. Data obtained from wet mount microscopy and pH paper can improve the accuracy of a diagnosis compared to diagnosis based on history and physical examination alone [6]. When assessing a patient with vaginal discharge, wet mount microscopy (if used) is almost always supplemented by **nucleic acid amplification testing (NAATs)** for gonorrhea, chlamydia, and trichomonas.

### 19.3.2 Etiologies of Vaginal Discharge

The causes of vaginal discharge can be divided into noninfectious and infectious etiologies (Table 19.1). The most common reason for vaginal discharge is **physiologic leukorrhea**. Many females experience an increase in discharge volume

**Table 19.1** Typical characteristics of the major causes of vaginal discharge

| | Physiologic leukorrhea | Allergic or chemical irritation | Bacterial vaginosis | Vulvovaginal candidiasis | Trichomoniasis | Mucopurulent cervicitis |
|---|---|---|---|---|---|---|
| Risk factors | None | Use of fragranced soap, bubble bath, perfume, latex condoms | Douche, new partner, multiple sexual partners, inconsistent condom use | Diabetes, antibiotic use, pregnancy, HIV disease, corticosteroid use | Multiple sexual partners, inconsistent condom use, low socioeconomic status | Adolescent age, new or multiple sexual partners, inconsistent condom use |
| Symptoms | None | Pruritus or burning may be present | Most asymptomatic, pruritus may be present | Pruritus, dysuria, dyspareunia | Pruritus, burning, dyspareunia, dysuria | Frequently asymptomatic, dyspareunia, irregular vaginal bleeding |
| Discharge | Clear or white, odorless | Clear, thin, odorless | Thin, white, or gray, malodorous, adherent to vaginal walls | Thick, white, cottage cheese-like, odorless | Gray/green, frothy, malodorous | Purulent or mucopurulent |
| Vulva | Normal | Erythema | Normal | Erythema, excoriations, fissures | Irritation | Normal |
| Cervix | Normal | Normal | Normal | Normal | Strawberry cervix | Friable |
| pH of discharge | <4.5 | <4.5 | >4.5 | <4.5 | 5–6 | <4.5 |
| *Wet mount* | | | | | | |
| WBCs<br>Epithelial cells<br>Organism | Occasional<br>Normal<br>Lactobacilli | Normal<br>Normal<br>Normal | Occasional<br>Clue cells<br>Bacteria adherent to cells | Increased<br>Normal<br>Budding yeast or pseudohyphae | Increased<br>Normal<br>Motile trichomonads | Increased<br>Normal<br>Normal |
| Whiff test | Negative | Negative | Positive | Negative | Positive | Negative |
| Preferred diagnostic test | None | None | POC test | None | NAAT | NAAT |
| Preferred treatment | None | Avoid offending agent | Metronidazole oral or topical, clindamycin topical | Topical antifungal creams or single-dose oral fluconazole | Single-dose oral metronidazole or tinidazole | Ceftriaxone *and either* doxycycline × 7 days *or* azithromycin single dose |
| Partner treatment | None | None | None | None | Recommended | Recommended |

Table adapted from Eliscu and Burstein [33]
*WBCs* white blood cells, *POC* point of care, *NAAT* nucleic acid amplification test

and a more stretchy consistency of the mucous discharge as a result of the luteinizing hormone surge that occurs just prior to ovulation [7]. Noninfectious etiologies of vaginitis include chemical irritation from fragranced soap, bubble bath, feminine washes, perfume, or scented sanitary pads; mechanical irritation from an intrauterine device or trauma; and allergic reactions to products such as latex condoms, lubricants, or topical medication. Individuals with mechanical, chemical, or allergic vaginal irritation typically have a thin, clear, odorless discharge with some erythema or burning of the vulva. Rarely, vesicles or bullae may be identified in patients with severe inflammatory reactions. Females using estrogen-containing contraceptives, such as oral contraceptive pills, may also notice a thin, clear, odorless discharge which is benign. Finally, retained foreign bodies such as a tampon, condom, or toilet paper can produce a bloody or purulent vaginal discharge with a foul-smelling odor. Symptoms of these conditions usually resolve once the offending agent is removed without any additional treatment.

The most common infectious etiology of vaginal discharge is **bacterial vaginosis (BV).** BV occurs when there is a shift in the normal vaginal bacteria flora from *Lactobacilli* species to a relative anaerobic state, dominated by microorganisms like *Gardnerella vaginalis*, *Mycoplasma hominis*, and *Mobiluncus* species [8]. BV is associated with a thin, homogenous, white or gray discharge that adheres to the vaginal wall and has a distinct fishy odor. BV is considered to be sexually associated, meaning sexual activity is a risk factor for developing the condition, but it is not transmitted by sexual contact. Accordingly, females who are not sexually active have significantly lower rates of BV when compared with those who are. Use of a douche increases the risk of developing BV because it has a tendency to disrupt the normal vaginal flora. Other risk factors associated with the development of BV include tobacco use and having a higher body mass index, while oral contraceptive use is inversely associated with BV risk [9]. Non-Hispanic Black women and women who have sex with women also have higher rates of BV when compared with the rest of the female population [9].

Bacterial vaginosis is diagnosed by physical examination in combination with results from wet mount microscopy and vaginal pH if 3 of the 4 following Amsel criteria are present: (1) presence of a thin, homogenous discharge coating the vaginal walls, (2) at least 20% of epithelial cells that are clue cells (epithelial cells studded with bacteria) on microscopy (Fig. 19.3), (3) vaginal fluid pH greater than 4.5, and (4) positive whiff test [4]. Sensitivity and specificity for diagnosing BV based on these Amsel criteria on examination and microscopy are 92% and 77%, respectively [9]. Alternatively, BV can be diagnosed using one of several available rapid point of care, **Clinical Laboratory Improvement Amendments** (**CLIA**)-waived tests. **CLIA** are US federal regulatory standards that apply to all diagnostic laboratory tests performed on humans in the United States unless granted a waiver. Such waivers require that the diagnostic test in question is simple to perform and that its results are easy to interpret (a home pregnancy test is a well-known example).

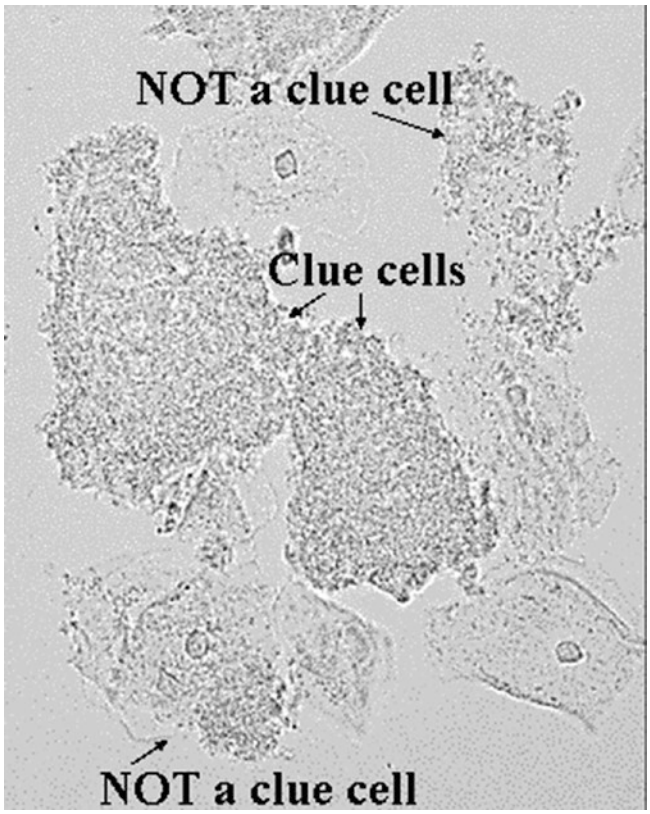



**Fig. 19.3** Wet mount microscopy showing clue cells consistent with bacterial vaginosis. (University of Washington STD Prevention Training Center)

Symptomatic females who are diagnosed with BV can be treated with oral or intravaginal metronidazole, oral or intravaginal clindamycin, or oral tinidazole [4]. Untreated BV has been shown to increase a female's risk of acquiring chlamydia or trichomonas [10], acquiring or transmitting HIV [11], and developing complications during pregnancy.

The second most common infectious etiology of vaginal discharge is **vulvovaginal Candidiasis (VVC)**, commonly referred to as a vaginal yeast infection. Seventy-five percent of females experience at least one episode [4]. Overgrowth of *Candida albicans* (or other *Candida* species), which is normally present in very small numbers, causes an acute inflammatory reaction leading to a thick, white, cottage cheese-like vaginal discharge, usually associated with intense vaginal itching. Affected females may also complain of dyspareunia and/or dysuria as a result of the inflammation. On physical examination, erythema, edema, and fissures of the vulvar and vaginal mucosa may be present. Risk factors for developing VVC include the use of oral contraceptives or an intrauterine device, pregnancy, immune suppression, use of oral antibiotics, and uncontrolled diabetes mellitus [12]. The diagnosis of VVC is often made on the history and physical examination findings alone. Suspected cases can be confirmed by visualization of pseudohyphae or budding yeast on wet mount microscopy (Fig. 19.4). Vaginal swab cultures for the presence of fungi is not helpful in the diagnosis since most women are colonized with small numbers of yeast. Multiple different

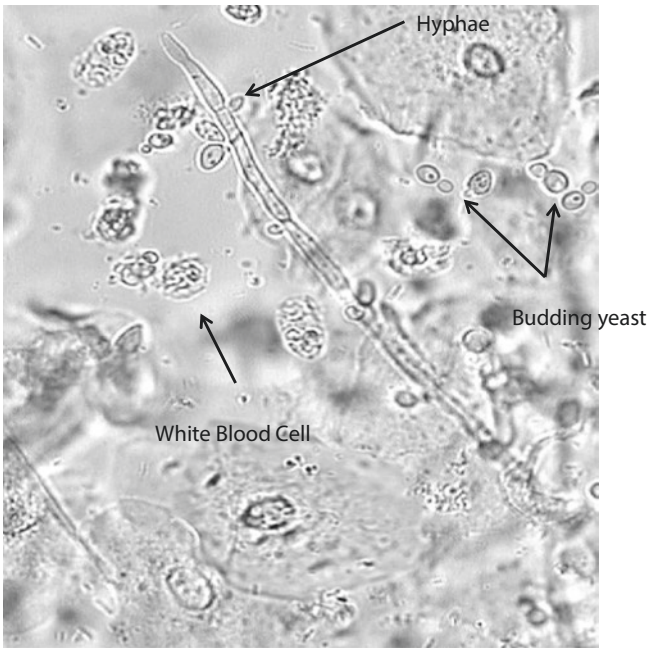



**Fig. 19.4** Wet mount microscopy demonstrating budding yeast and white blood cells consistent with vulvovaginal candidiasis. (University of Washington STD Prevention Training Center)

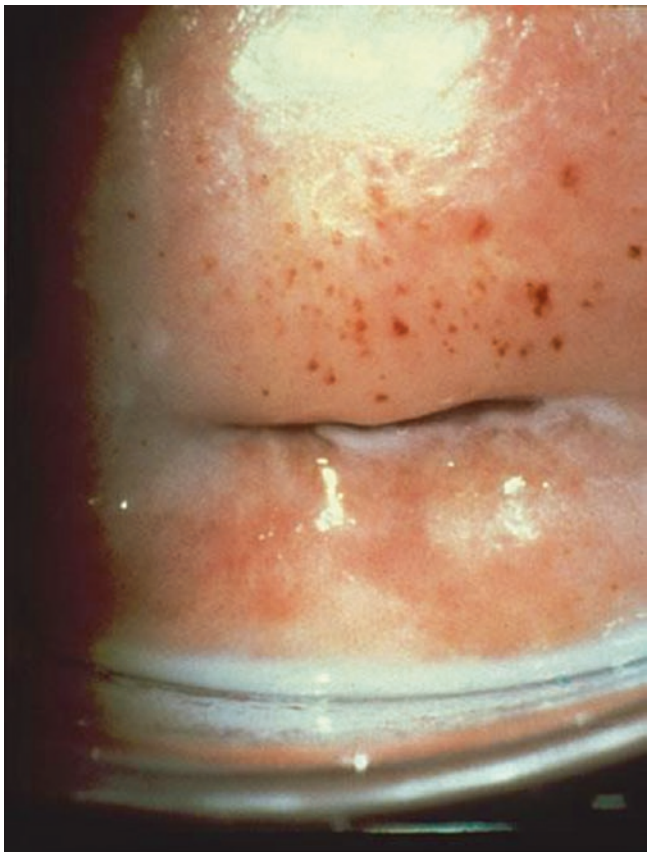


**Fig. 19.5** Strawberry cervix with punctate hemorrhages occasionally seen with *Trichomonas vaginalis* infections. (University of Washington STD Prevention Training Center)

regimens are available for treating VVC. Effective options include nonprescription antifungal medications for intravaginal use, such as clotrimazole 1% cream, prescription topical antifungal medications such as terconazole, and a single dose of oral fluconazole [4]. A single course of treatment is successful in more than 75% of cases with no significant differences in efficacy between the oral and topical regimens [13].

The third most common infectious etiology of vaginal discharge is **trichomoniasis**, a condition caused by the parasite *Trichomonas vaginalis* (TV). Trichomoniasis is the most prevalent nonviral STI worldwide affecting at least 2.3 million females of reproductive age in the United States [2]. Even these numbers likely underestimate the burden of disease since 85% of TV infections are thought to be minimally or completely asymptomatic. Symptomatic trichomoniasis typically presents with profuse, frothy, yellow-green, malodorous vaginal discharge, vaginal itching, pain, or dysuria [14]. There are clear racial disparities for the prevalence of TV infection with non-Hispanic black females being affected ten times more frequently than non-Hispanic White and Mexican American females [14]. TV infections are also more common with increasing age, higher number of sexual partners, younger age at sexual debut, lower educational level, and recent douching [14]. Physical examination findings can include a frothy vaginal discharge, vulvar and vaginal erythema, and punctate cervical hemorrhages, termed a "strawberry cervix" (Fig. 19.5) [15].

Historically, trichomoniasis was most commonly diagnosed by visualization of motile trichomonads on wet mount microscopy (Fig. 19.6) since it is easy to perform and offers rapid results at low cost. Wet mount microscopy, however, has a sensitivity of 60% or less, depending on the provider's level of experience [16]. The current gold standard diagnostic

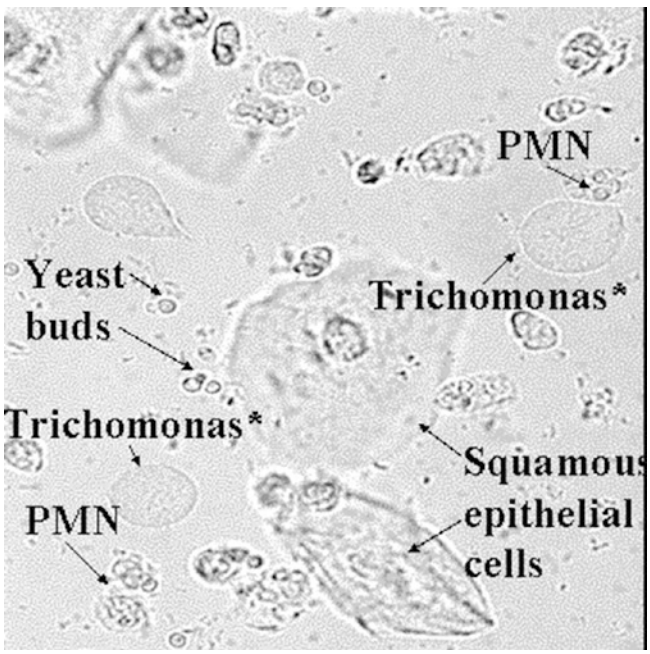



**Fig. 19.6** Trichomonads on wet mount microscopy. (Centers for Disease Control and Prevention Public Health Image Library)

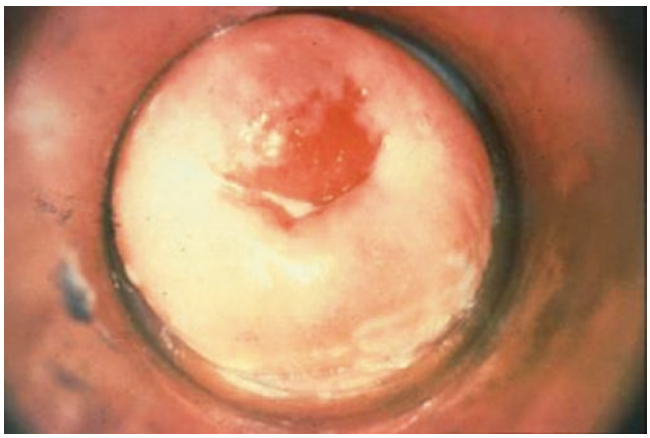
test for detecting trichomoniasis is NAAT [17]. At least one CLIA-waived point-of-care antigen detection test is also available (sensitivity 82–95% and specificity 97–100%) [4]. Culture for *Trichomonas vaginalis* is no longer used routinely because it has a slow turnaround time, is costly, and has a lower sensitivity than NAAT.

The recommended treatment for individuals diagnosed with trichomoniasis is a single oral dose of metronidazole or tinidazole; an alternative regimen is oral metronidazole twice daily for 7 days [4, 18]. In 2015, the Centers for Disease Control and Prevention (CDC) changed the treatment recommendation for HIV-infected individuals diagnosed with trichomoniasis from a single dose of metronidazole to a full 7-day course [4] in an effort to improve efficacy in this population. Sexual partners exposed to trichomonas within the prior 60 days should undergo complete STI testing and receive empiric treatment. Infected individuals should abstain from intercourse for at least 7 days following treatment both of themselves and their partner(s). Patients and sexual partners diagnosed with trichomoniasis should receive antibiotic treatment promptly since untreated individuals are at increased risk of acquiring and transmitting HIV infection [19] and for developing complications during pregnancy.

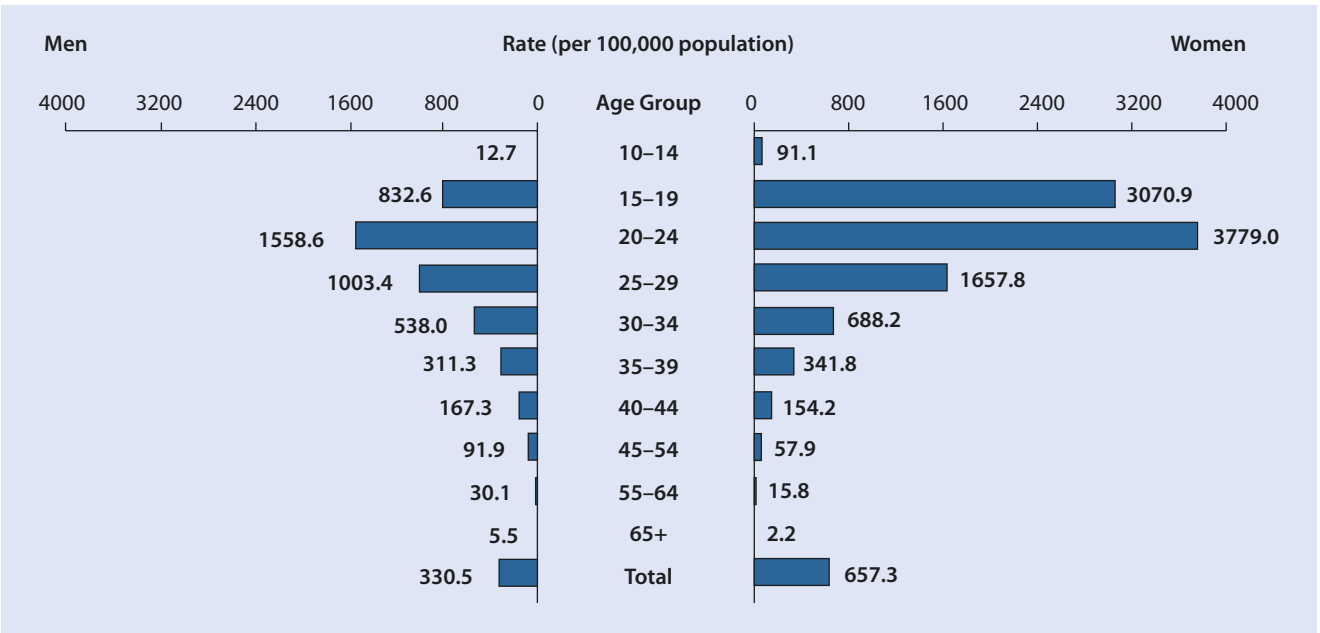
#### 19.3.2.1 Mucopurulent Cervicitis

The case presented in ▶ Call Out Box 19.3, involves a teenager with complaints of an odorless, yellow-green discharge and new intermenstrual bleeding. The patient's symptoms are *not* typical for BV, trichomoniasis, or VVC. Instead, her clinical examination findings of a friable cervix with mucopurulent discharge exuding from the cervical os are consistent with **mucopurulent cervicitis (MPC)** (◘ Fig. 19.7). *Chlamydia trachomatis* and *Neisseria gonorrhoeae* are the most common identified causes. Less commonly, *Herpes simplex virus* (type 2 more often than type 1) and *Trichomonas vaginalis* infection are confirmed. Retained foreign bodies and chemical irritation from douching are important noninfectious triggers for MPC. Even in the presence of MPC, females are frequently asymptomatic. Those who develop symptoms may complain of vaginal discharge, intermenstrual bleeding especially with intercourse, abdominal discomfort, and/or dyspareunia.

***Chlamydia trachomatis*** is the single most commonly identified causative organism of MPC and the most common reportable STI in the United States, with over 1.5 million cases in 2015. Like many other STIs, chlamydia infection is most prevalent among adolescents and young adults (◘ Fig. 19.8) [3]. Chlamydial infections are almost six times more common among non-Hispanic Black individuals and four times more common in American Indian and Alaskan



◘ **Fig. 19.7** Mucopurulent cervicitis with cervical erythema and purulent discharge from the cervical os. (CDC/NCHSTP/Division of STD Prevention, STD Clinical Slides)




◘ **Fig. 19.8** Rates of reported chlamydia cases by age and gender in the United States in 2015. (CDC 2015 STD Surveillance Chlamydia)

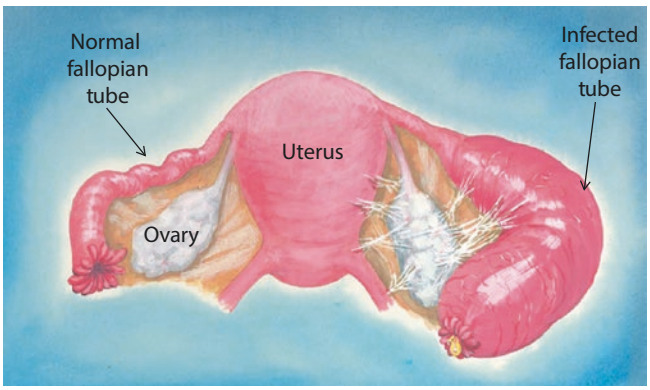
Natives when compared to White individuals [3]. Additional risk factors for contracting a chlamydia infection include younger age at sexual debut, having new or multiple sexual partners, a history of prior STI, and inconsistent use of barrier contraception. Tobacco use, BV infection, and infection with an oncogenic human papillomavirus type (such as type 16 or 18) are also considered risk factors for contracting a chlamydia infection [20].

Up to 75% of chlamydia infections among females are asymptomatic [21]. Symptomatic individuals may present with vaginal discharge, nonmenstrual vaginal bleeding occurring during sexual intercourse, and dysuria. The recommended diagnostic test for *Chlamydia trachomatis* is a NAAT performed on a sample collected from the cervix or vagina or on first-void urine (collected from the initial part of a urine stream). NAATs have replaced culture as the gold standard because, compared to culture, NAATs have higher sensitivity, are less expensive, can detect viable as well as nonviable organisms, require less stringent means of collection and transport, and are not as technically complex to run. In females, the biologic specimen with the highest sensitivity and specificity when using NAAT for the detection of chlamydia is a vaginal swab that can be collected by either the provider or by the patient herself. Assay sensitivity is the same whether the provider or the patient collect the swab, [22] and patients prefer to collect the sample themselves [23].

Females diagnosed with *Chlamydia trachomatis* should be promptly treated with a single oral dose of azithromycin or a 7 day course of doxycycline [4]. A test of cure is not recommended since these regimens are so highly effective. Treated individuals should, however, be retested 2–3 months later to identify those who have become reinfected as a result of resuming sexual activity with untreated partners or from a new partner or partners.

All sexual partners exposed to chlamydia within the prior 60 days should undergo complete STI testing and receive appropriate empiric treatment, *even if their chlamydia test is negative*. Following patient and partner treatment, individuals should abstain from sexual activity for at least 7 days. To facilitate treatment of exposed partners, providers may consider using **expedited partner therapy (EPT)** whereby providers prescribe treatment medications for the index patient's partner(s) without first examining them. EPT involves giving an index patient a prescription or dose of medication for their partner(s) accompanied by an explanation of the potential exposure, information about the prescribed medication including potential allergic reaction and adverse effects, possible sequelae of untreated infections, and recommendations for full STI testing. EPT is only recommended for partners exposed to gonorrhea or chlamydia and for those in heterosexual relationships since men who have sex with men have higher rates of concomitant STIs, like HIV and syphilis, which will remain undiagnosed if they receive EPT [4, 24]. As of July 2018, EPT is legally permissible in 42 US states, potentially allowable in 6 states, and prohibited in 2 states [25]. EPT should not be considered the optimal route for partner therapy, because empirically treated partners may be less likely to seek medical attention for a detailed STI evaluation looking for concomitant infections and less likely to seek risk reduction counseling.

Untreated chlamydia infections of the female genital tract can ascend leading to **pelvic inflammatory disease (PID)**. PID is defined as inflammation and infection of the endometrium, fallopian tubes, and/or ovaries (◘ Fig. 19.9). Females with PID may be asymptomatic or may present with pelvic pain, dyspareunia, postcoital bleeding, vaginal discharge, or dysuria. PID is diagnosed clinically when females present with pelvic pain, and their physical examination reveals either cervical motion tenderness, adnexal tenderness, or uterine tenderness. Additional signs and symptoms such as fever, presence of a friable cervix, or mucopurulent cervical discharge, in the context of a laboratory-confirmed chlamydia or gonorrhea infection, support the diagnosis of PID. **Consider the continued case presentation and associated questions in** ▶ Call Out Box 19.5**.**




◘ **Fig. 19.9** Acute salpingitis with adhesions extending to the ovary and uterus (PID). (Centers for Disease Control and Prevention STD Picture Cards)

**Call Out Box 19.5**

The patient described in ▶ Call Out Box 19.3 undergoes diagnostic testing. Wet mount microscopy performed on the vaginal fluid shows numerous white blood cells, no clue cells, no trichomonads or yeast, and a negative whiff test. The NAAT result from the cervical swabs was positive for *Chlamydia trachomatis* and negative for *Neisseria gonorrhoeae* and *Trichomonas vaginalis*. The teenager is treated with a single dose of azithromycin, and over the next 3 days, her vaginal discharge resolves. She was too embarrassed to disclose her infection to her sexual partner, doubting that he actually needed treatment since he has not complained of any symptoms. Two months later, the patient presented with vaginal discharge and significant pelvic pain of several days duration. On bimanual examination, she had cervical motion tenderness.

- What is the cause of her pelvic pain?
- What are the diagnostic criteria for this condition?
- What treatment should she receive?

When the patient was diagnosed with chlamydia 2 months ago, her boyfriend was asymptomatic. He remains asymptomatic. Should he be treated with antibiotics at this time? Should he have received treatment 2 months ago?

An uncommon but classic form of PID known as **Fitz-Hugh-Curtis syndrome** can also occur as a complication of ascending chlamydia infection. When a chlamydia (or gonorrhea) infection spreads beyond the genital tract to the liver capsule, it results in perihepatitis. Patients complain of right upper quadrant pain, nausea, and vomiting. Since symptoms are not localized to the genital tract and findings on pelvic examination, when performed, may not show evidence for typical PID, the initial differential diagnosis considered may unintentionally omit the possibility of an STI. PID, with or without perihepatitis, is associated with an intense acute inflammatory reaction that includes the formation of adhesions. Pelvic adhesions, including those that occur in the fallopian tubes, can lead to subsequent infertility, chronic pelvic pain, and increased risk of ectopic pregnancy. When inflammatory adhesions plaster a Fallopian tube onto an ovary, a small closed space is formed that can evolve into a tubo-ovarian abscess. Astute clinicians maintain a high level of suspicion for ascending pelvic infections, especially among high-risk females. Early diagnosis and effective antibiotic treatment will minimize the risk of developing scar tissue and its associated complications.

Since the majority of chlamydia infections are asymptomatic, yet may lead to substantial morbidity when left untreated, it is recommended that all sexually active females under 25 years of age undergo annual chlamydia screening [4, 26]. More frequent screening of higher risk females, such as sex-trade workers, those with multiple sexual partners, those reporting inconsistent condom use, and those with a history of a prior STI, may be indicated [4]. NAAT specimens for screening do not require a pelvic examination since the assay is sensitive and specific when performed on urine or self-collected vaginal swabs.

The second most common identified cause of mucopurulent cervicitis is ***Neisseria gonorrhoeae***. In 2015, nearly 400,000 cases of gonorrhea were reported in the United States with some of the highest rates occurring among 15–24-year-old females [27]. Risk factors for contracting gonorrhea include having new or multiple sexual partners, reporting inconsistent condom use, being of lower socioeconomic status, using alcohol or drugs, and having sex in exchange for money or drugs. Additionally, as with several other sexually associated and sexually transmitted infections, clear racial disparities for gonorrhea infections have been clearly documented. Gonorrhea is almost ten times more common among non-Hispanic Black individuals and four times more common among American Indian and Native Alaskan females compared to White females [27]. Like chlamydia, gonorrhea is frequently asymptomatic, with at least 45% of infections never presenting with symptoms [21]. When symptomatic, females infected with gonococcal infections may complain of vaginal discharge, irregular vaginal bleeding most commonly after intercourse, dysuria, dyspareunia, and abdominal pain. On physical examination, gonorrhea can produce the typical signs of mucopurulent cervicitis. Ascending gonorrhea causes PID with clinical signs, symptoms, and complications that are indistinguishable from PID caused by *Chlamydia trachomatis*.

Gonorrhea can be diagnosed by culture or NAAT. Compared to culture, NAATs are less labor intensive and may be performed on urine, cervical, or vaginal (provider or patient-obtained) specimens, whereas culture should only be performed on swabs taken from the cervix. NAATs are more sensitive in the detection of *Neisseria gonorrhoeae* infection compared to culture. Unlike culture, however, NAATs cannot provide any information about the organism's antibiotic susceptibility profile. CDC has been monitoring trends in antibiotic susceptibility of gonococcal strains since 1986 via the Gonococcal Isolate Surveillance Project (GISP). Surveillance first demonstrated a rise in rates of fluoroquinolone-resistant gonorrhea strains, from <1% in 1999 to almost 15% in 2007 [28], compelling the CDC to recommend against quinolones for the treatment of gonorrhea. In 2010, in response to concerns about increasing gonorrhea resistance to cephalosporins, CDC recommended dual treatment for gonococcal infections using both a cephalosporin and either azithromycin or doxycycline together. The goal of this rather unusual recommendation was to improve treatment efficacy and delay emerging resistance [29]. By 2015, GISP demonstrated increasing gonococcal resistance to cefixime, a third-generation oral cephalosporin. In response, CDC revised treatment recommendations for gonococcal infections to no longer include oral cefixime as a recommended cephalosporin treatment option. At the present time, the *only* recommended treatment for gonorrhea is dual therapy with a single intramuscular injection of ceftriaxone (a third-generation cephalosporin that is only given by injection) and a single oral dose of azithromycin [4]. Infected individuals should receive treatment as soon as possible to prevent complications such as PID and Fitz-Hugh-Curtis syndrome.

All sexual partners exposed to gonorrhea within the prior 60 days should receive complete STI testing along with empiric treatment, even if their gonococcal test is negative. Since the only recommended treatment course for gonorrhea involves an injection, use of EPT for the treatment of gonococcal infections has been revised. Optimal partner management involves STI testing and empiric treatment with ceftriaxone injection and an oral dose of azithromycin. For heterosexual individuals who are unlikely to receive appropriate treatment in a timely manner, EPT may be provided via a single oral dose of cefixime 400 mg and azithromycin 1 gram [30]. Treated individuals (including EPT-treated partners) should wait at least 7 days following treatment before resuming sexual intercourse and have a test for possible reinfection 2–3 months later. Additionally, providers should counsel patients about risk reduction practices including consistent condom use, limiting the number of sexual partners, and avoiding substance use.

### 19.3.3 Measures of Prevention

Adolescents and young adults account for about half of all new STIs in the United States, and the majority of these infections are asymptomatic. Those with asymptomatic

**Call Out Box 19.6**
**Recommendations for STI Prevention in Adolescents**
- Consistent condom use
- Limit number of sexual partners
- Avoid substance use
- Routine STI testing
- Recommend partners undergo routine STI testing
- Treat partners exposed to STIs empirically through the use of expedited partner therapy where allowed by law
- Receive a test of reinfection 2–3 months after STI treatment
- Provide nonjudgmental counseling and education on strategies to reduce risky behaviors

infections are unlikely to present for medical attention and are quite likely to unknowingly transmit their infection to sexual partners. Primary care providers should take the opportunity to elicit a confidential, detailed sexual history during the patient's preventative visits and during appointments for contraception, pregnancy testing, or evaluation of any gynecologic complaint. All sexually active females under 25 years of age should undergo routine screening for gonorrhea and chlamydia annually. Noninvasive specimens, such as urine or self-obtained vaginal swabs, can easily be collected and do not require performing a pelvic examination. Prevention messages should provide information about STIs and their transmission, teach males and females how to use condoms correctly and for every sexual encounter, and educate individuals to talk to their partners about safe sex [4, 31]. Such interventions are associated with lower rates of STIs and measurable reductions in risky sexual behaviors [32]. To further decrease transmitting infections, providers should encourage a comprehensive STI evaluation and empiric treatment for all exposed partners. For those partners who are unlikely to seek medical attention for empiric treatment, providers should consider practicing expedited partner therapy to maximize partner treatment rates [► Call Out Box 19.6].

## 19.4 Exercises

Please refer to the supplementary information section for answers to these exercises.

1. Match the etiologic agent of vaginal discharge with the most appropriate description:

| Pathogen | Characteristic finding |
|---|---|
| A. Physiologic leukorrhea | (i) Pruritic, thick, white, and odorless discharge, with excoriated vulva, pH < 4.5 |
| B. Vaginitis due to chemical irritation | (ii) Thin, white or gray, and malodorous discharge, pH > 4.5, clue cells |
| C. Bacterial vaginosis | (iii) Mucopurulent discharge from the os, friable cervix, many white blood cells on wet mount |
| D. Vulvovaginal candidiasis | (iv) Clear or white, odorless discharge with the presence of *Lactobacilli* |
| E. Trichomoniasis | (v) Gray, frothy, and malodorous discharge, positive whiff test |
| F. Mucopurulent cervicitis | (vi) Pruritic, clear, and odorless discharge with an erythematous vulva |

2. Which of the following statements is correct regarding routine STI screening recommendations for adolescent and young adult females?
   A. Females under 25 years of age should only undergo STI screening if they have symptoms such as vaginal discharge or irregular menstrual bleeding
   B. Endocervical specimens obtained during a pelvic examination are the only appropriate specimens for NAAT testing for gonorrhea and chlamydia infections
   C. All sexually active females under 25 years of age should undergo routine screening annually for gonorrhea and chlamydia using culture
   D. Nucleic acid amplification tests (NAAT) are the most accurate diagnostic tool for gonorrhea and chlamydia infections

3. A 17-year-old sexually active female presents to her doctor's office with new onset vaginal discharge. Her physician obtains a thorough history and performs a physical examination. Of the following, the most appropriate diagnostic test to perform is:
   A. Wet mount microscopy only
   B. Culture for both chlamydia and gonorrhea
   C. Nucleic acid amplification tests for *Chlamydia trachomatis, Neisseria gonorrhoeae,* and *Trichomonas vaginalis*
   D. Culture for bacterial vaginosis

4. A 20-year-old female presents with 3 days of yellow, odorless vaginal discharge. She has been sexually active with 2 male partners over the past month with inconsistent condom use. On physical examination, there is yellow-green, odorless discharge from the cervical os with cervical bleeding after gently touching it with a cotton swab. Wet mount microscopy is significant for an abundance of white blood cells but otherwise nondiagnostic. The patient was treated empirically with oral azithromycin and intramuscular ceftriaxone. NAAT testing is positive for *Chlamydia trachomatis* and negative for *Neisseria gonorrhoeae* and *Trichomonas vaginalis*. In addition to the empiric antibiotic treatment she was already given, all of the following should be performed *except*:
   A. Empiric partner therapy (possibly including expedited partner therapy)
   B. Test of cure in 3–4 weeks
   C. Test for reinfection in 3 months
   D. Risk reduction counseling

5. It is important to screen for, diagnose, and treat genital chlamydia infections in females because untreated infections are associated with which of the following:
   A. Fitz-Hugh-Curtis syndrome
   B. Infertility
   C. Chronic pelvic pain
   D. Increased risk of ectopic pregnancy
   E. All the above

## 19.5 Summary

- Vaginal discharge is a common medical complaint.
- Determining the etiology of a patient's vaginal discharge requires a detailed medical and sexual history, a complete physical examination, and performing appropriate diagnostic laboratory tests.
- The high prevalence of chlamydia and gonorrhea has led to the recommendation to perform annual screening for all females less than 25 years of age since the infections are often asymptomatic and are associated with substantial morbidity.
- To prevent serious sequelae such as PID, all identified STIs should be treated promptly according to the Centers for Disease Control and Prevention's most recent STD Treatment Guidelines.



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# Congenital and Perinatal Infections

## Newborn with Microcephaly, Blueberry Muffin Rash, and Hepatosplenomegaly

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**Learning Objectives**

- Recognize the common clinical manifestations of congenital and perinatal infections including those formerly known as "TORCH".
- Identify the most reliable laboratory methods to diagnose congenital infections.
- Understand the treatment options and long-term sequelae of the most common congenital and perinatal infections.

## 20.1 Introduction to the Problem

Congenital and perinatal infections can lead to a host of medical problems and life-long neurodevelopmental deficits. Early recognition of these infections is key to providing treatment for those where treatment is available and to ensure that the newborns are referred to each of the appropriate medical specialists needed. Neurodevelopmental problems are common sequelae for many of the infections, so early intervention services are often needed.

## 20.2 Definitions

**Vertical Transmission** - Transmission of an infection from mother to fetus or newborn during pregnancy, delivery, or shortly after birth.

**Congenital infection** - An infection that occurs in utero, acquired transplacentally. Evidence of the infection may be apparent at birth.

**Perinatal infection** - An infection that occurs during the birth process, acquired through direct exposure to maternal blood or body fluids at the time of delivery. Evidence of the infection is not apparent at birth. In some cases, the infection remains asymptomatic for months (human immunodeficiency virus) or years (hepatitis B, hepatitis C).

**TORCH** - Once a preferred acronym or mnemonic for the common causes of congenital infections. *T* was for congenital *t*oxoplasmosis; *O* was for *o*thers and included varicella, syphilis, and parvovirus B19; *R* was for *r*ubella, *C* was for *c*ytomegalovirus (CMV); and *H* for *h*erpes simplex virus (HSV). The list of pathogens now known to be associated with congenital and perinatal infections has expanded significantly, thereby reducing the utility of this memory aid. Neonatal HSV infections are only very rarely congenital. The vast majority occur perinatally, after the newborn is exposed to the virus during the birth process.

## 20.3 Basic Concepts: See Table 20.1

Congenital and perinatal infections can lead to fetal death, stillbirth, miscarriage, premature birth, and intrauterine growth restriction. The mode of vertical transmission for CMV, toxoplasmosis, rubella, syphilis, and parvovirus B19 is transplacental. These infections occur in utero. In contrast, the majority of neonatal herpes simplex virus infections occur as a result of exposure to genital secretions at delivery. Eruption of a vesicular rash during the first 4 weeks of life is very suspicious for perinatally acquired herpes simplex virus infection, but not all infants develop skin manifestations.

**Table 20.1** Pathogens with potential for vertical transmission from mother to fetus or child leading to congenital or perinatal infection

| Pathogen | Mode of transmission | Notes |
|---|---|---|
| Adenovirus | Perinatal | Cause of neonatal viral sepsis with fulminant hepatitis |
| Cyto-megalovirus | Congenital | Most common cause of congenital infection |
| Enteroviruses | Perinatal | Cause of neonatal viral sepsis with fulminant hepatitis |
| Hepatitis B virus | Perinatal | Largely preventable if exposed newborn is given both hepatitis B immune globulin and vaccine immediately after birth |
| Hepatitis C virus | Perinatal | Approximately 5% of infants born to infected mothers will become infected |
| Herpes simplex virus | Perinatal (very rare cases of congenital infection occur) | Primary maternal herpes simplex infection at the time of delivery is associated with the highest transmission rates (~50%) |
| Human immunodefi-ciency virus | Perinatal | Largely preventable if maternal viral load is well controlled; higher risk infants should receive antiretroviral medication for the first 6 weeks of life |
| Human T-lymphotropic virus I | Perinatal | Many who are infected remain asymptomatic for life, although some develop adult T-cell leukemia and others develop tropical spastic paraparesis |
| Human T-lymphotropic virus II | Perinatal | Most who are infected remain asymptomatic for life |
| Lymphocytic choriomeningi-tis virus | Congenital | Strong correlation with chorioretinitis and structural brain defects |
| Parvovirus B19 | Congenital | A cause of hydrops fetalis |
| Rubella virus | Congenital | Universal childhood vaccination has led to dramatic reductions in or elimination of congenital rubella syndrome |
| *Toxoplasma gondii* | Congenital | Protozoan transmitted to pregnant women upon exposure to contaminated meat or exposure to cat feces containing the parasite |

**Table 20.1** (continued)

| Pathogen | Mode of transmission | Notes |
|---|---|---|
| *Treponema pallidum* | Congenital | Maternal screening is important since more than half of infants with congenital syphilis are asymptomatic |
| Varicella-zoster virus | Congenital or perinatal | Congenital infection leads to severe scarring and contractures. Perinatal transmission leads to severe primary varicella in the newborn with an associated mortality rate of 30% |
| West Nile virus | Congenital | Rare. Leads to severe neurologic damage |
| Zika virus | Congenital | Associated with severe microcephaly, blindness, deafness, neurodevelopmental problems, and other congenital malformations |

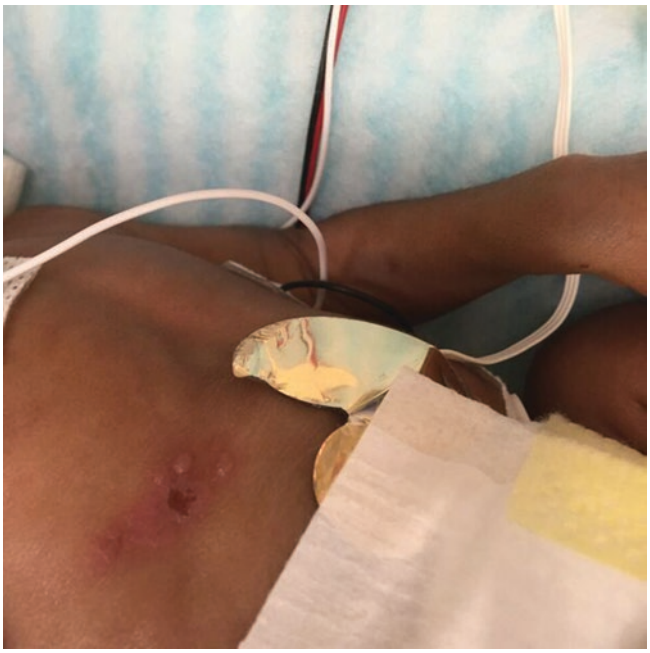


**Fig. 20.1** Shown is a 20-day-old infant who developed a cluster of vesicles on the abdomen 1 day ago. A polymerase chain reaction test performed on fluid that was collected by unroofing one of the lesions was positive confirming the suspected diagnosis of perinatal herpes simplex virus infection. (Image provided by Dr. Mayssa Abuali)

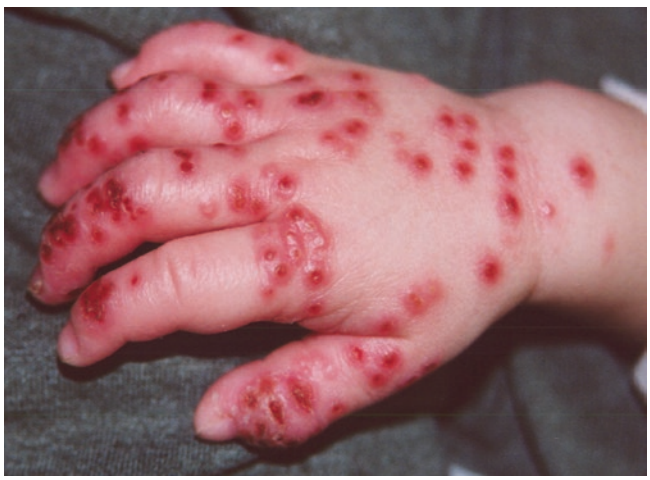


**Fig. 20.2** Shown is the right hand of a 14-day-old infant who developed a vesicular rash starting on day 11 of life. Testing confirmed the diagnosis of perinatal herpes simplex virus infection. (Image provided by Dr. David Clark)

The vesicles can be fairly subtle and clustered in one confined area (Fig. 20.1) or become more widespread (Fig. 20.2). Areas of skin previously disrupted by scalp electrode placement or circumcision are especially prone to inoculation and should be carefully inspected during the physical examination. Very rarely, true, in utero HSV infections occur. In general, maternal immunity plays a protective role, with transmission more likely to occur during primary (first time) maternal infections. For example, in neonatal HSV infection, perinatal transmission occurs in approximately 50% of circumstances where the mother's HSV infection is known to be her primary infection. Perinatal transmission of HSV from mother to infant falls to less than 2% of deliveries if the mother is known to have recurrence of past disease [1]. In many cases of congenital and perinatal infections, the pregnant woman recalls only a brief, self- limited illness during pregnancy if she recalls any symptoms at all.

Screening of pregnant women for syphilis during the first perinatal visit to the obstetrician and again at delivery is routine. Screening for maternal toxoplasmosis is common in Europe but is not included in standard obstetrical care in the United States. There is no reliable way to screen for primary CMV or HSV during pregnancy; however, if symptoms warrant and testing is performed that demonstrates active primary infection, antiviral therapy can be considered for the mother during the pregnancy to reduce the possibility of vertical transmission.

CMV is the most common vertically transmitted viral infection in the United States, with estimated infection rates of 0.5–1% of live births [1]. The clinical manifestations typically seen with congenital cytomegalovirus infection and other vertically transmitted infections that may become symptomatic at or shortly after birth are listed in Table 20.2 (Fig. 20.3).

Neonatal HSV infections are less common, occurring at a rate between 1 in 3000 and 1 in 20,000 live births [1]. Toxoplasmosis affects 1 in 10,000 live births [1]. The rates of congenital syphilis are now rising in the U.S., due to an increase in sexually acquired maternal infections, especially among women of childbearing age. Transmission of syphilis

**Table 20.2** Clinical manifestations of vertically transmitted infections by system

| | Neurologic | Ophthalmologic | Skin | GI | Skeletal | Other |
|---|---|---|---|---|---|---|
| Congenital cytomegalovirus infection | Microcephaly, hydrocephalus, periventricular calcifications, seizures, hearing loss, hypotonia | Chorioretinitis, vision loss | "Blueberry muffin" rash with associated petechiae and/or purpura | Hepatosplenomegaly, hepatitis, jaundice | Osteitis | Intrauterine growth retardation, anemia, thrombocytopenia |
| Congenital toxoplasmosis | Microcephaly, hydrocephalus, intracranial calcifications (not typically periventricular) seizures, hearing loss | Chorioretinitis, strabismus, blindness | Maculopapular rash | Hepatosplenomegaly hepatitis, jaundice, hepatic calcifications | | Intrauterine growth retardation, anemia, thrombocytopenia, pericarditis, pneumonitis, adenopathy |
| Congenital rubella syndrome | Microcephaly, hydrocephalus hearing loss, meningoencephalitis | Cataracts, glaucoma, retinopathy, microphthalmia | "Blueberry muffin" rash with associated petechiae and/or purpura | Hepatosplenomegaly, hepatitis, jaundice | Bony lucencies | Intrauterine growth retardation, anemia, thrombocytopenia, pneumonitis, congenital cardiac defects including patent ductus arteriosus, pulmonary artery stenosis, and coarctation of the aorta |
| Congenital syphilis | Meningitis, 8th nerve deafness (later, if untreated) | Chorioretinitis, glaucoma Interstitial keratitis (later, if untreated) | Maculopapular erythematous rash, turns coppery, involves palms and soles. Pemphigus syphiliticus-vesiculobullous lesions that rupture and macerate, petechiae | Hepatosplenomegaly hepatitis | Metaphysitis, periostitis, osteitis of the long bones. Later, if untreated: Saber shins, frontal bossing | Pneumonitis, anemia, snuffles (nasal discharge), lymphadenopathy Later, if untreated: Hutchinson teeth, mulberry molars, saddle nose deformity |
| Congenital varicella infection | Microcephaly, meningoencephalitis, seizures, cortical atrophy | Chorioretinitis, microphthalmia | Bullous lesions, hypopigmentation, scarring with disfiguring contractures | | Limb hypoplasia, absent digits | Hydronephrosis and hydroureter |
| Perinatal varicella infection | Meningoencephalitis | | Generalized vesicular rash, may be hemorrhagic | | | Pneumonia, viral sepsis. Associated with a 30% mortality rate |
| Congenital parvovirus B19 infection | Meningoencephalitis (very rare) | | | | | Intrauterine growth retardation, severe anemia, high-output heart failure with hydrops fetalis, thrombocytopenia |
| Perinatal herpes simplex virus infection | Meningoencephalitis, seizures, hypothermia, hearing loss | Keratitis, chorioretinitis, cataracts | Vesicles of the skin and mucous membranes | Hepatosplenomegaly, hepatitis, jaundice | | Inspect skin at scalp electrode and circumcision sites for vesicles and ulcers |
| Congenital herpes simplex virus infection | Microcephaly | Chorioretinitis, cataracts | | Fulminant hepatitis with hepatic failure | | Viral sepsis, pneumonia |
| Congenital Zika virus infection | Severe microcephaly, ventriculomegaly, subcortical calcifications, abnormal tone, deafness, blindness | Macular scarring, cataracts, optic nerve atrophy, microphthalmia | | | Skull collapse, joint contractures | |

Perinatal infection with hepatitis B and C viruses, HTLV-1 and 2, and HIV is almost always asymptomatic at birth and during early infancy. Of these, perinatally acquired HIV infection is the only one likely to lead to clinical manifestations during the first year of life.

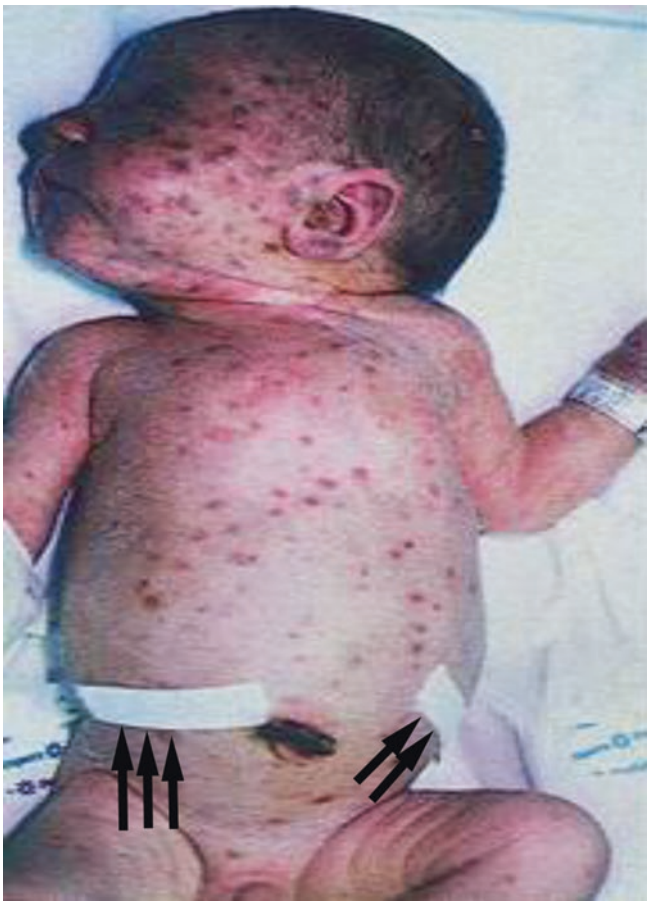


**Fig. 20.3** The term newborn shown here has the typical features of severe congenital cytomegalovirus infection including being small for gestational age, a generalized "blueberry muffin" rash, and massive hepatosplenomegaly. The edges of the liver and spleen are palpable well below the costal margins as identified by the white tape and highlighted with arrows. (Image provided by Dr. David Clark)

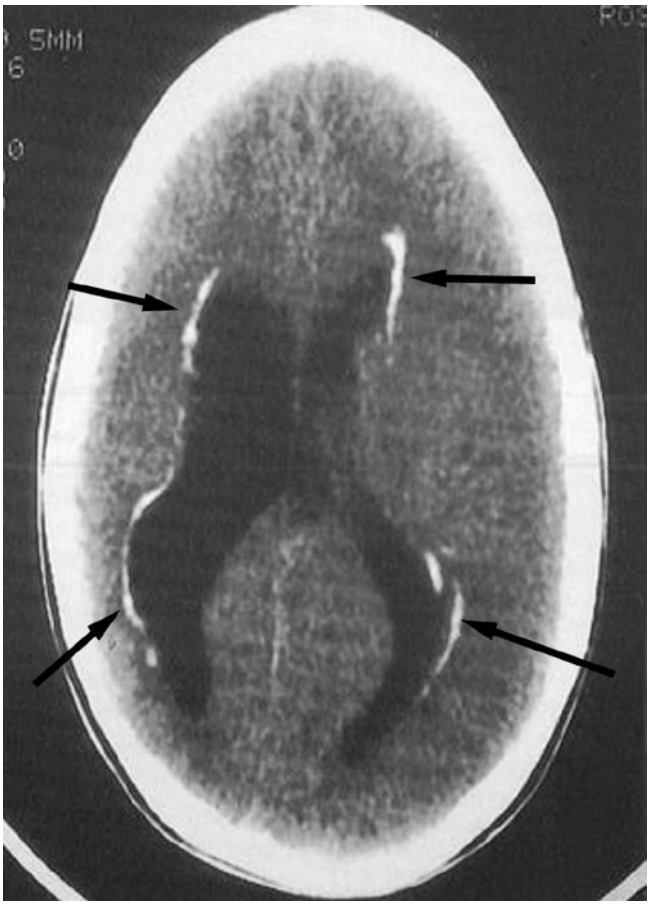



**Fig. 20.4** Computer tomography scanning of the brain of an infant with congenital cytomegalovirus infection. The lateral ventricles are dilated, indicating the presence of hydrocephalus. The location of the intracranial calcifications, highlighted by arrows, shows the classic periventricular distribution pattern that is so typical for congenital cytomegalovirus infection. (Image provided by Dr. David Clark)

is more likely to occur in untreated primary or secondary stage maternal syphilis, with estimated transmission rates of 60–100% [1, 2]. Universal childhood vaccination against rubella has led to such dramatic reductions in circulating virus that pregnant women who are susceptible to infection are no longer exposed to it in their communities. The vaccination efforts are so successful that congenital rubella syndrome has been eliminated from the U.S. [3]. Any woman of childbearing age who is found to be rubella seronegative should be offered rubella vaccine. Since the vaccine is contraindicated during pregnancy, women who are found to be rubella seronegative during their routine obstetrical perinatal care should be identified for vaccination immediately following the birth of their infant.

It is important to track the timing of maternal infections that have the potential to be transmitted to the fetus since the possibility of transmission and the outcome for the infected fetus vary depending on the gestational age at the time of infection. Both toxoplasmosis and CMV are more likely to be transmitted to the fetus if the maternal infection occurs later during pregnancy, but earlier fetal infection is associated with more severe disease manifestations. On the other hand, rubella infection is most easily transmitted to the fetus when the mother is infected early during pregnancy. Like toxoplasmosis and CMV, the manifestations of congenital rubella are more severe when the maternal infection occurs during the first 20 weeks of gestation [1, 3, 4]. Intracranial calcifications with or without hydrocephalus are seen in the most severe cases (Figs. 20.4, 20.5, and 20.6).

Most women of childbearing age had varicella infection (chicken pox) as a child or have been immunized. As such, they are immune to infection when they do become pregnant. Infants born at or near term to mothers with preexisting immunity are endowed with transplacental maternal antibody providing them with at least partial, passive protection from disease during infancy should they be exposed. Primary varicella infection during pregnancy is quite rare. Depending on the timing of the infection when it does occur, maternal disease can result in either congenital or perinatal infection in the infant. A pregnant woman who develops varicella during the first 20 weeks of gestation can transmit the infection to her fetus causing congenital infection. In utero infection can result in congenital varicella syndrome, adevastating condition where pox lesions form on fetal skin

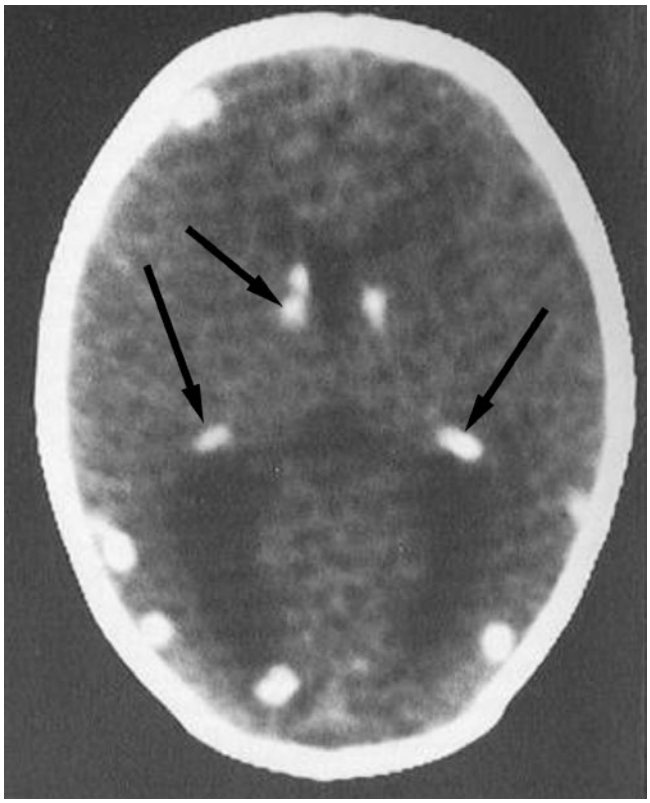


**Fig. 20.5** Computer tomography scanning of the brain of an infant with congenital toxoplasmosis. Several of the intracranial calcifications appear adjacent to the ventricular system (arrows), but others are scattered throughout the brain parenchyma. (Image provided by Dr. David Clark)

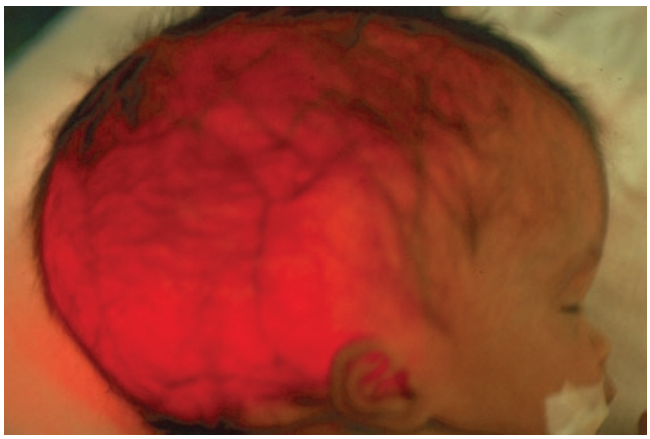


**Fig. 20.6** The infant shown was born with congenital toxoplasmosis complicated by severe hydrocephalus. Transilluminated light shines unimpeded through the fluid-filled skull indicating massive loss of normal brain parenchyma. (Image provided by Dr. David Clark)

tissue leading to extensive and severe contractures, sometimes with partial or complete loss of limbs or digits as the fetus grows [1] (Fig. 20.7). In contrast, when a pregnant woman develops primary varicella infection near the time of delivery, there is a very high risk for perinatal varicella infection. Perinatal transmission is highly probable when the

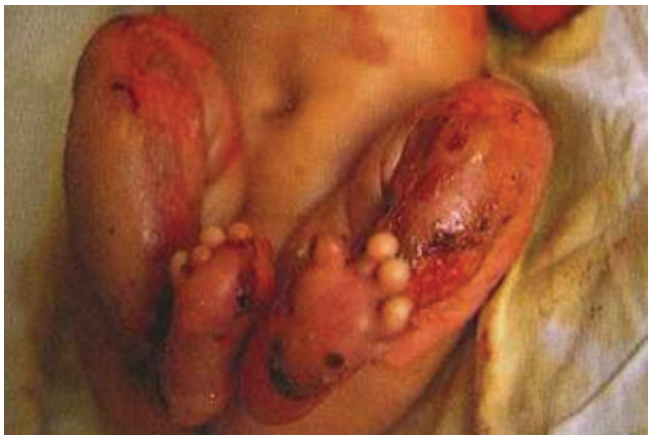


**Fig. 20.7** This newborn was infected with varicella-zoster virus while in utero. The pox lesions are now gone but are responsible for the partial loss of several toes, residual scarring, and limb contractures. (Image provided by Dr. David Clark)

mother develop varicella 5 days before or up to 2 days after delivery. Newborns who develop varicella after perinatal exposure to the virus develop severe, disseminated disease associated with a 30% mortality rate [1, 5]. Prevention of perinatal varicella infection is achieved by administering varicella immune globulin to the newborn, thereby providing immediate passive protection to the infant. As such, prevention of this potentially deadly neonatal infection has three requirements:

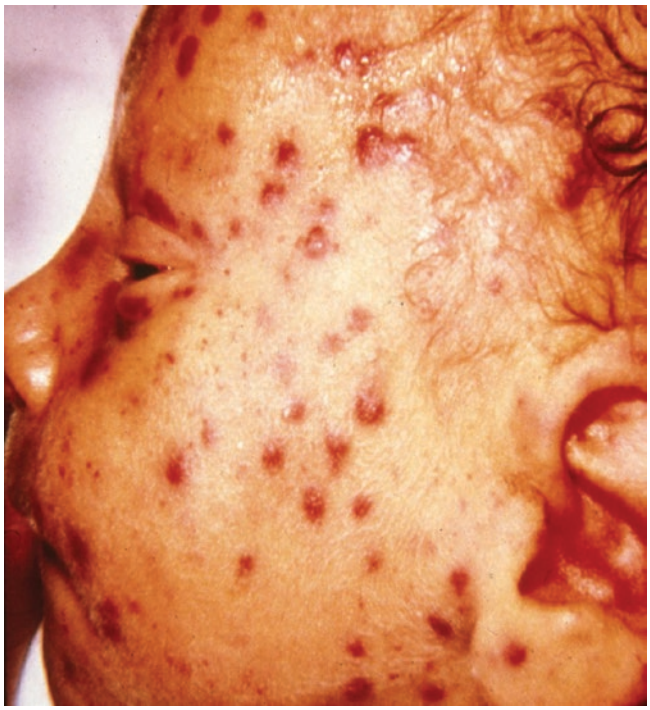
1. The mother's rash illness must be recognized as chicken pox. This has become more challenging in the post-vaccine era since many providers have never seen primary chicken pox.
2. The provider who recognizes the maternal varicella infection must be aware that the timing of the maternal infection places her newborn in a life-threatening situation that requires immediate action.
3. Varicella immune globulin must be administered promptly.

Fifth disease, caused by infection with parvovirus B19, is one of the classic numbered febrile exanthems of childhood. Adults who were infected during childhood retain immunity from reinfection, and those who have not yet been infected remain susceptible. As such, maternal infection during gestation is uncommon, estimated to occur at a rate of about one per hundred pregnancies, with a vertical transmission rate of approximately 35% [4]. While in utero infection with parvovirus B19 is rare, it can be life-threatening and is associated with substantial morbidity. Parvovirus B19 targets and kills erythroid progenitor cells resulting in a transient arrest of erythropoiesis. When this occurs under conditions of very high erythroid cell turnover, arrested erythrocyte production can lead to severe anemia. In utero infections have potential to cause such severe anemia that the fetus develops high-output heart failure with associated fetal hydrops. The risk of fetal loss is between 2% and 6% [1].

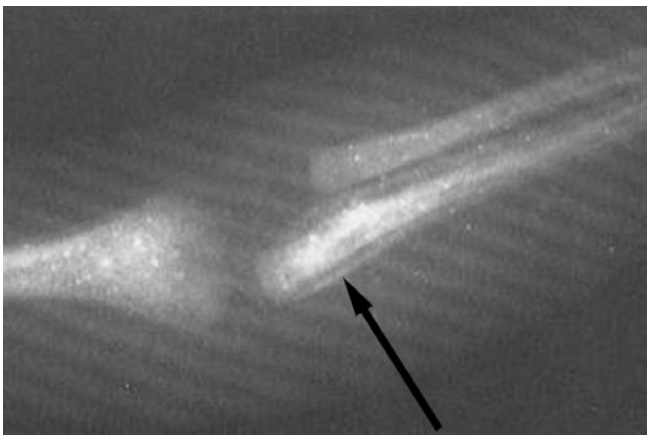
Zika is an emerging flavivirus that was first appreciated as a cause of severe congenital infections during the 2015 epidemic that began in Recife, Brazil, and quickly spread across South, Central, and parts of North America including the island countries of the Caribbean Sea (refer to ▶ https://wwwnc.cdc.gov/travel/page/world-map-areas-with-zika) [2, 6]. Zika virus is spread to human primarily through the bite of the *Aedes aegypti* mosquito, but person-to-person spread through sexual contact and from mother to fetus is now well appreciated. Clinically, maternal infection may present as a brief, mild, febrile rash illness associated with conjunctivitis, but 80% of all infections are so mild that they go unrecognized. Surveillance studies demonstrate that approximately 10% of infants born to mothers who contract Zika infection during pregnancy are born with symptomatic congenital Zika disease. The manifestations of congenital Zika infection range from asymptomatic illness to severe disease with microcephaly and multisystem organ involvement.

Vertically transmitted HSV infection, like varicella infection, can result in either congenital or perinatal disease in the infant. Vertical transmission of HSV from mother to infant at the time delivery is quite common, but congenital, in utero HSV infection is very rare. Perinatal HSV infection becomes evident during the first 4–6 weeks of life. Three distinct clinical presentations are well appreciated. Some infants develop disease localized to their skin, eyes, and mucous membranes (SEM), some developed meningoencephalitis, and others present with disseminated infection. The recommended length of antiviral treatment and overall prognosis differ according to the clinical presentation [1, 7].

A congenital infection is easily suspected when an infant is born with classic, severe signs such as microcephaly or blueberry muffin rash, but not likely suspected at all in a term newborn with a normal physical examination. CMV is the most common cause of congenital viral infection, but only 10% of infected newborns are symptomatic at birth with the "classic" TORCH signs and symptoms of microcephaly, growth restriction, blueberry muffin rash, and hepatosplenomegaly [1, 4, 8] [◘ Fig. 20.8]. Infants born with severe manifestations of congenital cytomegalovirus or rubella infection have typically suffered significant prenatal insults to their central nervous systems. Many have also experience near arrest of bone marrow-associated hematopoiesis. In an effort to compensate for poorly functioning bone marrow, earlier fetal sources of hematopoiesis, including the liver, the spleen, and the skin, resume prior activity. Clinically, the resulting hepatosplenic extramedullary hematopoiesis results in hepatosplenomegaly. Similarly, the presence of multiple islets of bluish-gray bone marrow elements scattered throughout the skin gives the newborn the appearance of a blueberry muffin (◘ Figs. 20.3 and 20.8). Symptomatic disease is seen in ~40% of newborns with congenital syphilis infection, again placing the majority of those infected in the asymptomatic category [9, 10]. Osteitis is a typical finding on radiographs performed on newborns with congenital syphilis (◘ Fig. 20.9), even if bone involvement is not suspected based on symptoms. Similarly, between 70 and 90% of newborns with congenital toxoplasmosis are asymptomatic at birth. It is not uncommon for a newborn with a congenital infection, who is asymptomatic at birth, to develop symptoms later in infancy [1, 9, 11].



◘ **Fig. 20.8** This infant has a classic blueberry muffin rash. The scattered, widespread, raised purpuric lesions are small islets of extramedullary hematopoiesis. As the bone marrow recovers over time, the rash fades, a process that takes weeks to months. (Image provided by Dr. David Clark)



◘ **Fig. 20.9** A plain radiograph of the elbow was taken as part of a complete skeletal series during the evaluation of an infant with suspected congenital syphilis. Periosteal inflammation (arrow) is a classic radiographic finding of congenital syphilis. Serologic testing was used to confirm the diagnosis. (Image provided by Dr. David Clark)

Many of these vertically transmitted infections have the potential to cause serious long-term sequelae especially hearing loss, vision loss, and neurodevelopmental deficits, even when the newborn is initially asymptomatic. Hearing loss secondary to congenital CMV infection occurs among 50% of symptomatic and 15% of symptomatic infants. Loss of

hearing acuity is often progressive, with up to half of all children experiencing gradual deterioration during their first 5 years of life [1]. Chorioretinitis secondary to both CMV and toxoplasmosis has the potential to reactivate later in life, particularly during subsequent periods of immune suppression. The hearing impairment, visual disturbances, learning disabilities, and mental retardation associated with congenital toxoplasmosis can first manifest years later, even in infants who appear completely normal at birth [1, 11]. Similarly, late-onset manifestations are common among infants with congenital rubella infection [3, 4]. In untreated congenital syphilis, interstitial keratitis can first manifest between 5 and 20 years of age and 8th nerve deafness between 10 and 40 years of age [1]. Together with the presence of peg-shaped central incisors (Hutchinson teeth), these three late-onset manifestations of congenital syphilis are referred to as the Hutchinson triad [1, 9, 4].

The frequency of neurologic difficulties following perinatal infection with herpes simplex virus is dependent on the initial clinical presentation of the infection. Only 5% of infants who presented with isolated disease of the skin, eyes, and/or mucous membranes will develop long-standing neurologic problems. In contrast, 54% of those who present with central nervous system infection, and 38% of those who presented with disseminated disease go on to develop serious neurodevelopmental sequelae [7]. Recurrent herpes skin lesions occur in 50% of those who survive the initial infection [1]. Close follow-up with serial neurodevelopmental, auditory, and ophthalmologic testing is important for all newborns known to have a perinatal or congenital infection.

Diagnostic laboratory testing is available to confirm the various causes of vertically transmitted infections (Table 20.3). After the diagnosis is established, additional testing is typically necessary to document the extent of the infection, including which organ systems are involved, to monitor the course of the disease over time, and to monitor both for the effectiveness of treatment and for any toxicities associated with some fairly complex anti-infective regimens.

Diagnostic testing for congenital toxoplasmosis is particularly complex. Optimally, both maternal and newborn antibody titers should be performed in the Palo Alto Medical Foundation Toxoplasma Serology Laboratory [1, 12, 13]. Although traditional instruction teaches that only IgG isotype antibodies cross the placenta, newborn blood may contain small, but measurable amounts of maternal IgM and IgA antibodies. If maternally derived toxoplasma-specific IgM antibodies are present, they are typically cleared within 5 days of birth. Similarly, small amounts of maternally derived IgA antibodies will be cleared by 10 days of life. If initial testing of the infant is performed during that time period is positive for either isotype, a new sample should be collected and tested later to confirm the diagnosis [1, 12, 13]. *Toxoplasma gondii* can also be isolated using mouse inoculation of tissue or fluid collected from the placenta, umbilical cord, cerebrospinal fluid, urine, or blood [1, 12, 13]. Avidity testing of detected anti-toxoplama IgG antibodies can also be performed on positive samples from the mother and the infant. The advantage of doing so allows relative timing of the maternal infection, including whether the infection likely took place prior to the start of the pregnancy of concern.

**Table 20.3** Diagnostic testing for vertically transmitted infections

| Infection | Diagnostic tests to consider |
|---|---|
| Congenital toxoplasmosis | Serum IgG, IgM, and IgA from infant and mother<br>Polymerase chain reaction testing of serum, urine, and/or cerebrospinal fluid<br>Hepatic transaminases and bilirubin<br>Complete blood count<br>Neuroimaging |
| Congenital cytomegalovirus | Urine vial culture during the first 3 weeks of life<br>Urine or saliva polymerase chain reaction testing<br>Hepatic transaminases and bilirubin<br>Complete blood count<br>Neuroimaging |
| Perinatal herpes simplex virus infection | Polymerase chain reaction testing of blood<br>Polymerase chain reaction testing of cerebrospinal fluid<br>Polymerase chain reaction testing of conjunctivae, oropharynx, rectum, and any skin lesions present<br>Viral culture from any of the above anatomic fluids or sites<br>Hepatic transaminases and bilirubin<br>Complete blood count<br>Neuroimaging |
| Congenital rubella syndrome | Serum rubella IgM<br>Serial testing of serum rubella IgG<br>Throat or nasal polymerase chain reaction testing or viral culture<br>Less commonly, polymerase chain reaction testing or viral culture of urine or cornea (cataract)<br>Echocardiogram<br>Hepatic transaminases and bilirubin<br>Complete blood count<br>Neuroimaging |
| Congenital syphilis | Quantitative rapid plasma reagin on mother and infant<br>Fluorescent treponemal antibody absorption (FTA-ABS) IgM test<br>If available<br>Fluorescent treponemal antibody absorption (FTA-ABS) IgG test<br>To confirm maternal infection<br>No useful diagnostically for the infant infant<br>Venereal Disease Research Laboratory<br>(VDRL) test of cerebros<br>pinal fluid<br>Hepatic transaminases and bilirubin<br>Complete blood count<br>Plain radiographs of the long bones<br>Chest radiograph if indicated<br>Serial quantitative rapid plasma reagin to verify treatment effectiveness |

**Table 20.3** (continued)

| Infection | Diagnostic tests to consider |
|---|---|
| Congenital or perinatal varicella infection | Polymerase chain reaction testing of vesicle fluid<br>Direct fluorescent antibody testing of vesicle fluid<br>Viral culture of vesicle fluid, with roll tube inoculation at the bedside<br>Hepatic transaminases and bilirubin<br>Neuroimaging if indicated |
| Congenital parvovirus B19 infection | Antenatal polymerase chain reaction testing on amniotic fluid<br>Postnatal polymerase chain reaction testing on blood<br>Serum parvovirus B19 IgM<br>Complete blood count |
| Congenital Zika virus testing | Polymerase chain reaction testing on blood<br>Polymerase chain reaction testing on urine<br>Polymerase chain reaction testing on cerebrospinal fluid<br>Serum Zika virus IgM<br>Cerebrospinal fluid Zika virus IgM<br>Neuroimaging |

Cytomegalovirus infection must be diagnosed in the first 3–4 weeks of life in order to be considered congenital, as postnatal infection through breastfeeding is not uncommon [1]. The gold standard diagnostic test is a standard roll tube urine culture for virus, but the virus is slow-growing so a result can take several weeks to become available. The shell vial spin amplification technique allows a diagnosis to be confirmed in 48 to 72 h. The shell vial technique includes inoculation of the urine sample onto target cells known to be permissive to cytomegalovirus replication (MRC-5 human lung fibroblasts are commonly used). The sample is then subjected to a low-speed centrifugation. The purpose of the "spin" is not to pellet the virus onto the cells—that would require a much stronger g-force that is not typically available in clinical microbiology laboratories. Instead, the low-speed centrifugation alters the target cell membrane in a manner that renders it much more permissive to virus attachment and internalization. Following a 48–72-h incubation, the target cells are then stained with a cytomegalovirus-specific antibody tagged with fluorescein. Infected target cells are easily identified under fluorescence microscopy (Fig. 20.10). Polymerase chain reaction testing may also be used to detect the presence of virus in urine. Various tests are also available to detect virus in blood samples or to identify virus-specific IgM from serum samples. Positive results using techniques performed on blood samples during the first 3–4 weeks of life are highly suggestive of, but not diagnostic for, congenital cytomegalovirus infection [1, 8]. A confirmed diagnosis depends on the detection of virus in the newborn's urine during the first 3–4 weeks of life. It is important to make this distinction because postnatal infections do not lead to later sequelae such as progressive sensory neural hearing loss [1].

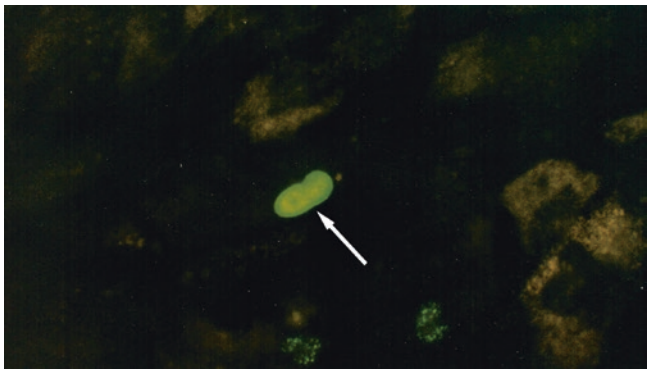


**Fig. 20.10** Shown is a shell vial cell monolayer stained with a fluorescein-tagged anti-cytomegalovirus antibody that recognizes a viral protein expressed in the nucleus of infected cells. The fluorescent green oval structure identified with the arrow is the nucleus of a cytomegalovirus-infected cell indicating that the virus was present in the urine sample that was used to inoculate the target cells 48 h earlier. (Image provided by Mrs. Cynthia Bonville)

The diagnosis of congenital syphilis can be challenging since it relies on the accurate interpretation of several different serologic results. Results from serologic tests that are not specific for *T. pallidum*, known as the rapid plasma reagin (RPR) titer and the Venereal Disease Research Laboratory (VDRL) result, are most useful; however, confirmatory testing using an antibody test that specifically detects anti-*T. pallidum* antibodies is necessary to confirm syphilis in the mother. Assuming that maternal syphilis infection has already been confirmed using a *T. pallidum*-specific test, the most useful test to perform on the newborn is the RPR. A newborn RPR titer that is fourfold higher than the mother's result strongly suggests that the infant has been infected. Additional testing should then be performed, an appropriate treatment regimen administered (usually with intravenous penicillin), and follow-up arranged. A fluorescent treponemal antibody absorption (FTA-ABS) IgG test result from a newborn is not helpful since it will be positive due to the presence of transplacental maternal IgG antibodies. In circumstances where congenital syphilis is suspected at birth and the placenta is available for testing, the detection of spirochetes in placental samples using dark-field microscopy or direct fluorescent antibody staining is confirmatory [9, 10].

Eighty percent of acute Zika virus infections are asymptomatic, including infections that occur during pregnancy. As such, all pregnant women who live or travel to Zika virus-endemic areas should undergo screening for infection. Polymerase chain reaction-based testing is useful for those who may have been exposed during the last 2-week period. Serologic testing should be used if the exposure was more than 2 weeks ago. If congenital Zika infection is suspected prenatally, the diagnosis can be confirmed by polymerase chain reaction-based testing on fluid collected during amniocentesis. Postnatally, testing of newborns is ideally performed during the first 48 h of life.

## 20.4 Prevention of Vertically Transmitted Infections

Anti-infective treatments are only available for a small number of vertically transmitted infections (Table 20.4). Moreover, any in utero infection that leads to microcephaly has already caused severe, irreversible damage to the developing brain that cannot be reversed with a course of postnatal anti-infective therapy emphasizing the need to optimize all available preventive measures. Routine childhood vaccination programs have greatly reduced the possibility that susceptible pregnant women will be exposed to varicella or rubella infection in their communities. Maintaining high community vaccination rates is key to this success. Susceptible women of childbearing age can receive vaccines against both rubella and varicella. When a pregnant woman is found to be seronegative, however, she should wait to be vaccinated until after she gives birth. The rationale for waiting is that both vaccines contain live attenuated viruses, so they have not been tested for safety or effective during pregnancy. The charts of women discovered to be seronegative during their pregnancy should therefore be flagged as a reminder to administer the required vaccine(s) after delivery but during the birth hospitalization.

**Table 20.4** Available anti-infective treatments for vertically transmitted infections

| Infection | Anti-infective treatment |
|---|---|
| Congenital toxoplasmosis | Pyrimethamine plus sulfadiazine plus folinic acid orally for 1 year |
| Congenital cytomegalovirus | Valganciclovir, orally for 6 months |
| Perinatal herpes simplex virus infection | Acyclovir<br>Intravenous for 14 days for SEM disease<br>Intravenous for 21 days for CNS disease<br>Each followed by 6 months of oral suppression |
| Congenital rubella syndrome | None available<br>Prevention is key. Maintain high rubella vaccination rates. Any woman found to be seronegative for rubella during pregnancy should be immunized immediately after delivery |
| Congenital syphilis | Aqueous penicillin G intravenous or procaine penicillin G intramuscular for 10 days<br>Alternatively, benzathine penicillin G intramuscular as a single dose under low-risk circumstances |
| Congenital or perinatal varicella infection | Acyclovir, intravenous<br>Prevention is key. Maintain high varicella vaccination rates. Varicella-zoster immune globulin should be administered to newborns exposed to maternal varicella 5 days before or 2 days after delivery |
| Congenital parvovirus B19 infection | No antiviral medications are available. Support using in utero and/or postnatal red blood cell transfusions can be life-saving |
| Congenital Zika virus infection | None available |

The screening for and treatment of mothers who are found to have syphilis during pregnancy is essential in the prevention of congenital syphilis. Since women may continue to experience the same risk factors for syphilis after treatment, some become reinfected with *T. pallidum* during the same pregnancy. Ongoing assessments during each prenatal visit are essential so that any subsequent infections are also identified and treated appropriately.

Cytomegalovirus is one of nine herpesviruses known to infect humans. Like other herpesviruses, cytomegalovirus establishes latency following primary infection. Asymptomatic reactivation of virus replication is very common, particularly among young children. Common sense dictates that regular handwashing is prudent for the prevention of most infections and is especially important after contact with body fluids from others, something that occurs regularly in every household that includes young children. Pregnant woman should also be counseled to avoid sharing utensils or food with children, advice that only seems practical when including children who are not her own.

In an effort to prevent infection with *Toxoplasma gondii*, all pregnant women should know to avoid consuming meat that is raw, undercooked, or smoked. Consumption of any freshly hunted wild game is strongly discouraged. Pregnant women should also avoid any potential direct exposure to cat litter, cat litter boxes, soil, raw shellfish, and untreated water. If direct exposure to any of these potential sources of toxoplasmosis is unavoidable, wearing gloves and paying close attention to careful handwashing after removing the gloves are essential. Immunocompromised individuals who are diagnosed with chronic parvovirus B19 infection and those experiencing a parvovirus B19-associated aplastic crisis are actively shedding virus. Pregnant women, such as healthcare workers, should avoid exposure to such individuals. Pregnant women who are regularly exposed to children with the classic rash of fifth disease, such as mothers, teachers, doctors, and other members of the healthcare team, need not be concerned about developing parvovirus B19 infection because otherwise healthy children are no longer contagious by the time their rash appears.

Travel to Zika virus-endemic areas is strongly discouraged during pregnancy. Women living in or traveling to such areas should be counseled on mosquito avoidance and abstaining from sexual activity with someone known to be infected. Women who discover that they are pregnant during or after at-risk travel should be screened for Zika infection. Those who are found to be infected with Zika virus require serial prenatal ultrasounds to monitor the growth parameters, including the head circumference, of the fetus. Infants born to mothers known to have had Zika virus infection during pregnancy, including those who appear completely healthy at

birth, need careful longitudinal neurodevelopmental follow-up that includes regular testing of hearing and vision.

Pregnant women who are diagnosed with acute toxoplasmosis are treated with the antibiotic spiramycin from the time they are diagnosed until delivery. This approach successfully reduces the risk of vertical transmission and helps to attenuate symptom severity in infected neonates born to those mothers [1].

Pregnant women who are found to have active genital herpes during labor are less likely to transmit the infection to their infant if they are delivered by Cesarean section.

## 20.5 Exercises

Please refer to the supplementary information section for answers to these exercises.

1. Match each of the listed clinical findings, 1 through 6, with one or more of the listed infection(s), A through G, where they are most typically seen:

| Clinical finding | Infection |
|---|---|
| 1. Periventricular calcifications | A. Perinatal herpes simplex virus |
| 2. Blueberry muffin rash | B. Congenital syphilis |
| 3. Osteochondritis | C. Congenital toxoplasmosis |
| 4. Vesicular rash | D. Congenital varicella |
| 5. Skull collapse | E. Congenital rubella |
| 6. Limb hypoplasia | F. Congenital Zika virus |
| 7. Microcephaly | G. Congenital cytomegalovirus |

2. An infant female was born vaginally at 37 weeks gestational age to a G1P0 mother with Apgar scores of 8 and 9. On physical examination, she was small for gestational age, with a birth weight of 1.690 kg, birth length of 44.5 cm, and birth head circumference of 30.5 cm. An ophthalmology examination showed no evidence of chorioretinitis or cataracts, but she failed her newborn hearing screen on two separate attempts. Laboratory testing revealed elevated serum hepatic transaminases and thrombocytopenia. You suspect that congenital cytomegalovirus infection is the cause of her constellation of signs and symptoms. Of the following options, the best laboratory test to confirm your suspicion is:
   A. Serum cytomegalovirus Ig M antibody by enzyme-linked immunoassay.
   B. Serum cytomegalovirus Ig G antibody by complement fixation.
   C. Polymerase chain reaction testing of whole blood for cytomegalovirus.
   D. Urine culture for cytomegalovirus using shell vial amplification technique.

3. Match each anti-infective regimen (1 through 4) to each of the infection(s) (A through F) it is used to treat (more than one may apply):

| Anti-infective | Infection |
|---|---|
| 1. Acyclovir | A. Congenital Zika |
| 2. Valganciclovir | B. Congenital toxoplasmosis |
| 3. Pyrimethamine plus sulfadiazine | C. Congenital syphilis |
| 4. Penicillin G | D. Congenital varicella<br>E. Congenital cytomegalovirus<br>F. Perinatal herpes simplex |

4. The "blueberry muffin rash" is a classic physical examination finding in infants with congenital rubella or congenital cytomegalovirus infection. Of the following options, a full-thickness skin biopsy obtained from one of the lesions appearing like a blueberry would have microscopic findings most consistent with:
   A. Cyanotic foci with alternating zones of apoptosis and necrosis.
   B. Dermal fibroblasts teeming with viral inclusion bodies.
   C. Hematopoietic elements of bone marrow.
   D. Perivascular inflammation with hemorrhages.

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# Infections of the Central Nervous System

Contents

# Myelitis and Acute Flaccid Paralysis

## Rapid Onset of Severe Muscle Weakness

*Jana Shaw*




J. Domachowske (ed.), *Introduction to Clinical Infectious Diseases*,
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**Learning Objectives**

1. List common and uncommon causes of transverse myelitis, acute flaccid myelitis, and acute flaccid paralysis.
2. Describe clinical manifestations of acute flaccid myelitis and acute flaccid paralysis.
3. Explain the differences between acute flaccid myelitis and acute flaccid paralysis.
4. Apply knowledge of acute flaccid paralysis to guide timely diagnostic evaluation.

## 21.1 Introduction to the Problem

This chapter will focus on disorders which present with acute paralysis of the extremities and/or muscles innervated by the cranial nerves: acute transverse myelitis, acute flaccid myelitis, and acute flaccid paralysis.

Acute transverse myelitis (ATM) is characterized by acute progressive paresis, with sensory deficits and loss of bowel and bladder function. Transverse myelitis is a rare condition with incidence of 1–2 per 1 million [1]. Its prevalence has a bimodal distribution with peaks occurring between the ages of 10 and 19 years and 30–39 years [2]. Although both genders are affected, in children less than 10 years of age, the condition is twice as common among boys. Gender appears to play a less important role after adolescence [1]. New diagnostic criteria for ATM were published by the Transverse Myelitis Group Consortium in 2002 (see Table 21.1) [3]. The most recent criteria distinguish between idiopathic and disease-associated causes of ATM and include clearly defined inclusion and exclusion criteria for the diagnosis.

Patients with ATM present with limb weakness, bladder and bowel dysfunction which may include urinary retention, urinary or bowel incontinence, or constipation. Bilateral leg weakness is the most common clinical finding of ATM, followed by paraplegia and upper extremity weakness [4]. Paresthesias or numbness are present in approximately 70–90% of patients [4]. The illness typically peaks in 1 week's time and rarely progresses beyond 4 weeks. Muscle strength and deep tendon reflexes change over time. The initial muscle weakness is followed by muscle spasticity, and depressed or absent deep tendon reflexes later become hyper-reflexive [5]. The presence of a positive Babinski sign during a comprehensive neurologic examination suggests upper motor neuron dysfunction. A careful physical examination may also provide clues to the cause of illness. For example, a patient with varicella-zoster virus-associated ATM may have "shingles," a characteristic dermatomal rash that is seen with varicella-zoster virus reactivation.

During the summer of 2014, US public health officials received reports of increased number of children presenting for medical care with acute flaccid myelitis (AFM). The condition being described was quite similar to acute poliomyelitis. A majority of the children had been recently diagnosed with an acute respiratory viral infection, ultimately found to be caused by enterovirus D68. Attempts to isolate the virus from cerebrospinal fluid (CSF) were unsuccessful and the precise role of enterovirus D68 in triggering or causing AFM remains unclear. Many of the patients with AFM during enterovirus D68 season have not recovered neurologically. Certainly, the biologic plausibility exists that this virus has neurovirulent properties similar to poliovirus and has been the cause of most of all of these illnesses.

**Table 21.1** Criteria for idiopathic acute transverse myelitis[b]

| Inclusion criteria | Exclusion criteria |
|---|---|
| Development of sensory, motor, or autonomic dysfunction attributable to the spinal cord<br>Bilateral signs and/or symptoms (though not necessarily symmetric)<br>Clearly defined sensory level<br>Exclusion of extra-axial compressive etiology by neuroimaging (MRI or myelography; CT of spine not adequate)<br>Inflammation within the spinal cord demonstrated by CSF pleocytosis or elevated IgG index or gadolinium enhancement. If none of the inflammatory criteria is met at symptom onset, repeat MRI and lumbar puncture evaluation between 2 and 7 day following symptom onset meet criteria<br>Progression to nadir between 4 h and 21 day following the onset of symptoms (if patient awakens with symptoms, symptoms must become more pronounced from point of awakening) | History of previous radiation to the spine within the last 10 year<br>Clear arterial distribution clinical deficit consistent with thrombosis of the anterior spinal artery<br>Abnormal flow voids on the surface of the spinal cord c/w AVM<br>Serologic or clinical evidence of connective tissue disease (sarcoidosis, Behcet's disease, Sjogren's syndrome, SLE, mixed connective tissue, disorder, etc.)[a]<br>CNS manifestations of syphilis, Lyme disease, HIV, HTLV-1, mycoplasma, other viral infections (e.g., HSV-1, HSV-2, VZV, EBV, CMV, HHV-6 enteroviruses)[a]<br>Brain MRI, abnormalities suggestive of MS[a]<br>History of clinically apparent optic neuritis[a] |

*AVM* arteriovenous malformation, *SLE* systemic lupus erythematous, *HTLV-1* human T-cell lymphotropic virus-1, *HSV* herpes simplex virus, *VZV* varicella-zoster virus, *EBV* Epstein-Barr virus, *CMV* cytomegalovirus, *HHV* human herpes virus

[a]Do not exclude disease-associated acute transverse myelitis

[b]Copied from Transverse Myelitis Consortium Group [3]

## 21.2 Definitions

**Acute transverse myelitis (ATM)** – refers to inflammation of the spinal cord spanning across it entire width. It can affect one or several segments of the spinal cord [6]. It manifests with both sensory and motor complaints including pain, sensory loss, paresthesias, muscle weakness, paralysis, and/ or bladder and bowel dysfunction depending on the cord level(s) affected.

**Acute flaccid paralysis (AFP)** – is a relatively sudden onset of weakness involving one or more limbs with accompanying reduction in muscle tone and deep tendon reflexes and was the sine qua non for diagnosis acute paralytic poliomyelitis.

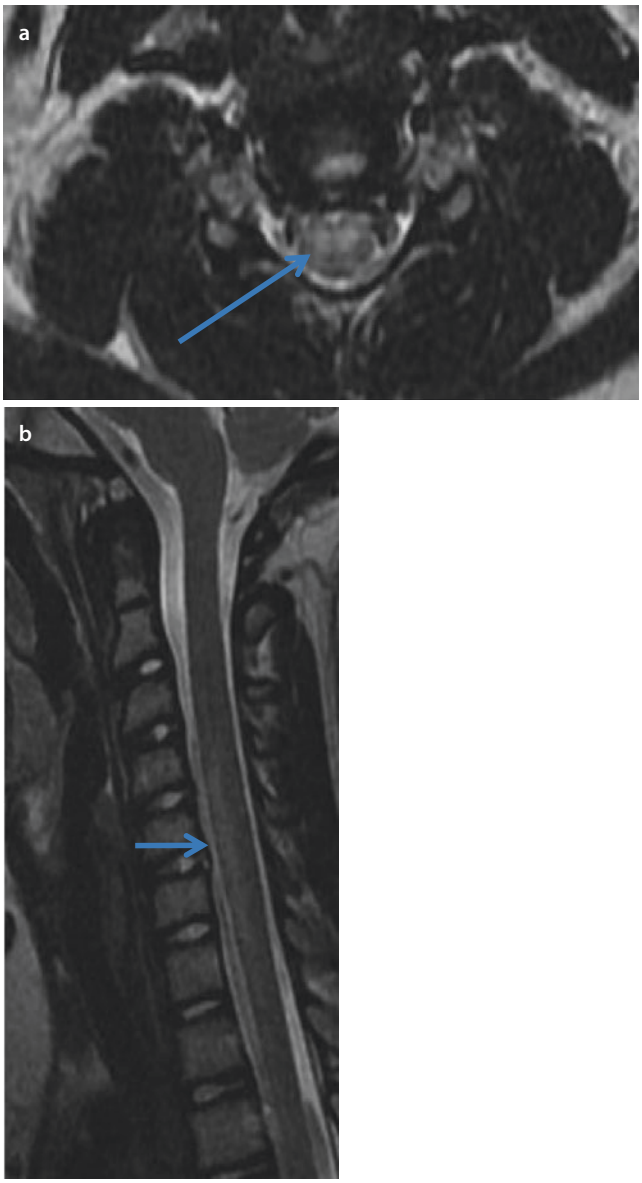
**Acute flaccid myelitis (AFM)** – refers to acute onset of focal limb weakness with associated MRI changes in the spinal cord. MRI changes are largely restricted to gray matter, spanning one or more spinal segments. Together these features constitute a definite case according to the current working definitions. A probable case of AFM is diagnosed in a patient who has acute onset of focal limb weakness along with cerebrospinal fluid (CSF) cellular pleocytosis [7].

## 21.3 Basic Concepts

### 21.3.1 Acute Transverse Myelitis

Individuals presenting with symptoms of acute myelopathy should initially be evaluated to rule out a structural or anatomic cause. Intrinsic or extrinsic masses that can compress the spinal cord and cause acute neurological symptoms include tumors, hematomas, and abscesses. Magnetic resonance imaging (MRI) performed with gadolinium contrast is the study of choice and should be performed as soon as possible because structural compressive lesions require urgent neurosurgical intervention. The MRI may show swelling of cord and T2 hyperintense signals usually affecting the central gray matter. Enhancement with gadolinium contrast may be seen. Acute-phase MRI changes in a patient with ATM are shown in ◘ Fig. 21.1. Chronic MRI changes consisting of mild cord atrophy and myelomalacia in the anterior (motor) horn are shown in ◘ Fig. 21.2. If no structural lesions are found, the patient should undergo lumbar puncture to differentiate between inflammatory and noninflammatory conditions affecting spinal cord function. At a minimum, the CSF evaluation should include a total cell count and differential, total protein and glucose levels, testing for oligoclonal bands and IgG index, and a cytopathology examination.

A CSF pleocytosis together with an absence of any structural defect is most suggestive of an inflammatory condition such as infection, post-infectious demyelination, or a collagen vascular disorder. A careful and full neuroimaging study that includes the spinal cord and the brain will allow determination of whether the inflammatory abnormalities are isolated to a single area or are multifocal. Brain MRI with gadolinium contrast should therefore be included for all patients with suspected ATM even in the absence of specific cerebral symptoms [5]. Demyelination in the brain that is limited to optic nerve tract, together with abnormal spinal cord findings is most consistent with neuromyelitis optica. Demyelination beyond the optic nerve, with or without spinal cord changes, is characteristic for acute demyelinating encephalomyelitis or multiple sclerosis. A finding of discrete focal spinal cord demyelination is most consistent with ATM. In the presence of fever, vomiting diarrhea, cough, rash, or meningismus, an infectious etiology for the ATM is probable [5]. Involvement of other organs such as the kidneys, skin, or joints suggests that the cause of the neurologic problem is secondary to an autoimmune condition, such as systemic lupus erythematosus or Sjögren syndrome rather than an infection. The recommended diagnostic evaluation for ATM is guided by the suspected cause(s) and is summarized in ◘ Table 21.2. Treatment options, where available, are dependent on the underlying cause.




◘ **Fig. 21.1** **a** Shown are magnetic resonance images of the spine of an 8-year-old with transverse myelitis. The axial fast spin-echo T2-weighted image of the cervical spine demonstrates increased signal intensity in the spinal cord, mainly in the anterior horns at C5 and C6. **b** Sagittal fast spin-echo T2-weighted imaging of the cervical spine demonstrates mild cord swelling and increased signal intensity in the anterior spinal cord extending from lower C4 to upper C7 (b). No enhancement was evident. (Courtesy of Dr. Kalliopi Petropoulou)

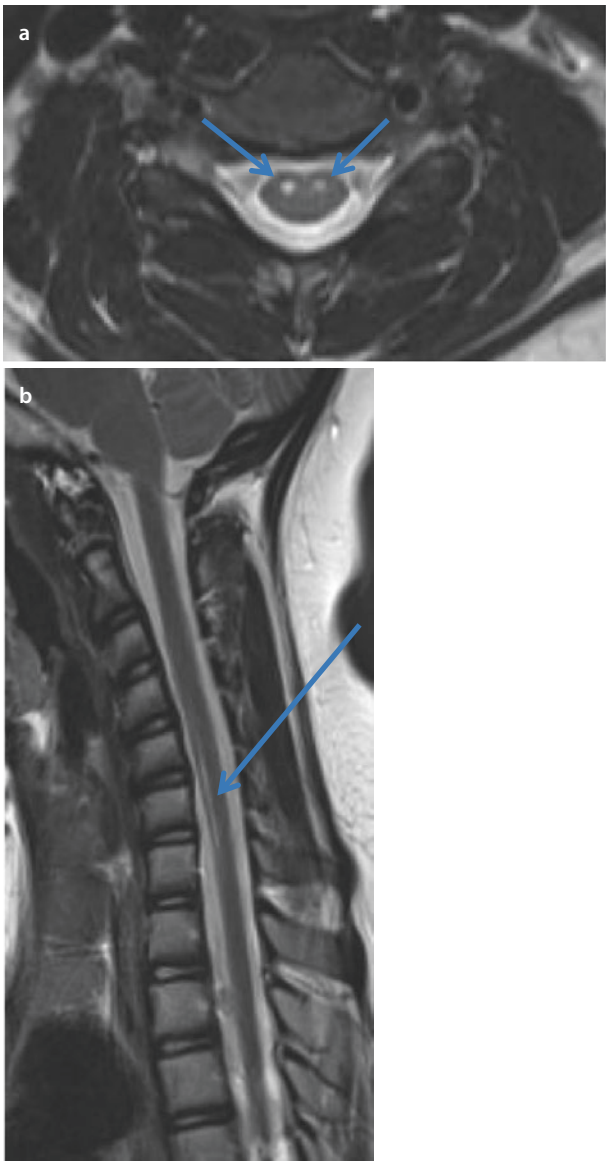



**Fig. 21.2** **a** Follow-up magnetic resonance images of the same patient obtained 2 years after her initial diagnosis of transverse myelitis. Axial fast spin-echo T2-weighted images demonstrate mild cord atrophy and myelomalacia in the anterior horn (arrows). **b** Sagittal fast spin-echo T2-weighted images demonstrate mild cord atrophy and myelomalacia in the anterior cervical cord. (Courtesy of Dr. Kalliopi Petropoulou)

**Table 21.2** Suggested diagnostic workup for recurrent central nervous system demyelinating disorders and systemic autoimmune disorders associated with acute transverse myelitis[a]

| All patients | Suggestive of neuromyelitis optica | Also consider |
|---|---|---|
| Brain MRI with gadolinium<br>CSF oligoclonal bands<br>Antinuclear antibodies<br>Antiphospholipid antibodies<br>Serum NMO-IgG | Ophthalmology consultation<br>Visual evoked potentials<br>Formal visual field testing | Angiotensin-converting enzyme (serum, CSF)<br>Other autoantibodies<br>Anti-dsDNA<br>Anti-La<br>Anti-Ro<br>Anti-smith |

*CSF* cerebrospinal fluid, *MRI* magnetic resonance imaging, *NMO* neuromyelitis optica
[a]From Holder and Lotze [5], with permission of Elsevier

**Box 21.1 Conditions that mimic idiopathic transverse myelitis[a]**

- Direct infectious myelopathies
- Extramedullary compressive lesions
- Epidural abscess
- Epidural hematoma
- Extramedullary tumors
- Guillain-Barré syndrome
- Intramedullary spinal cord trauma
- Astrocytoma
- Ependymoma
- Ischemia and infarction
- Syringomyelia
- Radiation injury
- Traumatic spinal cord injury
- Vascular malformation

[a]From Holder and Lotze [5], with permission of Elsevier

### 21.3.2 Acute Flaccid Paralysis (AFP) and Acute Flaccid Myelitis (AFM)

AFP can be caused by a range of infectious, autoimmune, and acquired etiologies. Infections that are known to cause AFP include polioviruses; live-attenuated vaccine strain polioviruses; non-polio enteroviruses; West Nile virus; St Louis encephalitis virus; Cache Valley, La Crosse virus, and other California serogroup viruses; Powassan and Japanese encephalitis virus; Eastern and Western equine encephalitis viruses; Zika virus; herpes simplex viruses; parvovirus B19; influenza virus; human immunodeficiency virus; Lyme disease; cat scratch disease; campylobacteriosis; and botulism [8]. Patients presenting with acute onset of weakness or cranial nerve palsy without sensory deficit and obvious cause should be evaluated for a polio-like illness caused by these agents. Approach to the diagnostic evaluation of AFP is summarized in ▶ Box 21.1. Polioviruses 1, 2, and 3 were once the classic and common cause of acute weakness leading to paralysis in children. Due to successful global polio vaccination programs, polioviruses have been eliminated from the Western hemisphere, poliovirus 2 has been globally eradicated, and polioviruses 1 and 3 remain endemic only to Afghanistan and Pakistan.

Guillain-Barré syndrome has now become the most common cause of AFP among previously healthy infants and children [9] with an annual incidence of 0.34–1.34 cases per 100,000 persons aged 18 years or less [10]. The most common form of GBS is acute inflammatory demyelinating polyradiculopathy (AIDP). Individuals develop neurologic symptoms 2–4 weeks after a benign febrile respiratory or gastrointestinal infection [11]. The proposed mechanism is the one of molecular mimicry when the immune response to recent infection (such as campylobacter-associated gastroenteritis) results in the production of antibodies that cross-react with self-epitopes [12]. The resulting immune response then leads to acute polyneuropathy. Infections identified as triggers for the development of GBS include campylobacteriosis, cytomegalovirus, human immunodeficiency virus, Epstein-Barr virus, *Mycoplasma pneumoniae*, and influenza [13, 14]. No matter which pathogen triggers the development of GBS, the signs and symptoms are identical. GBS is characterized by pain and gait difficulty followed by ascending paralysis. Younger children, not able to express themselves, may present with refusal to walk and irritability due to pain. Weakness begins distally in the lower extremities. The weakness advances in ascending fashion, usually quite symmetrically, unlike polio which is more typically an asymmetrical ascending paralytic disease. The most advanced cases of GBS lead to paralysis of the muscles of respiration requiring that the patient be supported with artificial mechanical ventilation [15]. Autonomic dysfunction and cranial neuropathy are present in nearly one-half of individuals with GBS [16]. On physical examination, deep tendon reflexes are absent, and weakness is symmetrical and is ascending in nature. The severity of weakness ranges from mild inability to walk to complete paralysis. The diagnosis of GBS relies on a compatible clinical presentation, supportive findings from CSF analysis, electrodiagnostic studies, and neuroimaging findings. The CSF analysis will show and elevated total protein concentration with a normal CSF leukocyte count. An MRI with gadolinium contrast may reveal enhancement of the spinal or cranial nerve roots, but this finding has limited specificity. Electrodiagnostic studies are sensitive and specific for GBS and differentiate between axonal or demyelinating conditions [17]. Antibodies against epitopes in Schwann cell surface membrane or myelin proteins or epitopes in the axonal membrane are available commercially and assist in diagnosis of the demyelinating forms of GBS. Some patients with GBS respond to treatment with intravenous immunoglobulin infusions or plasma exchanges. Prognosis for full or near full recover is excellent, but some patient do suffer life-long sequelae [18].

AFM, a form of AFP, is a complex clinical syndrome characterized by the rapid onset of weakness in association with MRI changes found in the grey matter of one or more spinal cord segments [19]. This illness resembles acute paralytic poliomyelitis. Viruses causing (or once causing) AFM include West Nile virus; polioviruses 1, 2, and 3; non-polio enteroviruses (enterovirus A71 is an excellent example); Japanese encephalitis virus; and Zika virus [20]. Poliomyelitis virus remains a classic, now extremely rare cause of AFM. The effects of poliovirus infection on the anterior motor horn cells of the spinal cord and will be detailed here to illustrate the symptoms and approach to diagnosing AFM from poliovirus or any of the other causes listed above.

Poliovirus infection is known to cause a range of symptoms. The vast majority of infections are either asymptomatic or mildly symptomatic of a viral gastroenteritis with complaints of headache, fever, nausea, abdominal pain, or diarrhea. Neuroinvasion with paralysis occurs in fewer than 1% of individuals infected with poliovirus. When it does occur, it most typically affects the lower motor neurons innervating the legs [21]. With ascending paralysis, involvement of the respiratory muscles can lead to life-threatening consequences and a requirement for ventilatory support. Bulbar paralysis (paralysis of one or more of the lower cranial nerves VII–XII) presents with dysphagia, dysarthria, and difficulty handling secretions. Improvement of the paralysis generally occurs gradually during the period of recovery, but weakness or paralysis that is still present after 60 days usually remains permanent.

Diagnosis of acute paralytic poliomyelitis is confirmed by detection or isolation of poliovirus from clinical specimens (i.e., detection of the virus by PCR from CSF, identification of the virus from stool or from a nasopharyngeal culture). Viral cultures from nasopharyngeal and stool specimens should be obtained as soon as possible and within 2 weeks of the onset of illness [22]. Two stool specimens should be collected 24 h apart to increase the sensitivity of detection.

During the summer of 2014, public health authorities in the United States were alerted of clusters of polio-like illnesses of unknown etiology. The Children's Hospital of Colorado reported 12 cases of AFM and cranial nerve dysfunction with brainstem lesions occurring among children between August and October of that year. The majority of the children had preceding febrile illnesses and symptoms of an upper respiratory tract infection [23]. Of the 12 children reported, 10 had meningismus; 10 had flaccid limb weakness, mainly proximal, asymmetric, and hyporeflexic; 10 had cranial nerve dysfunction; 11 had spinal cord lesions in the central gray matter involving the anterior motor horn cells; all had CSF pleocytosis; and all had persistent motor deficits during follow-up. No pathogens were identified from CSF samples.

Since the summer of 2014, the US CDC confirmed 277 cases of AFM between August 2014 and December 2016, with 136 cases occurring during 2016 alone [24]. Although many of AFM cases were preceded by mild respiratory illness due to enterovirus D68, extensive testing has not iden-

tified this virus or any other pathogen in the CSF. The role of enterovirus D68 in the pathogenesis of AFM remains unclear.

## 21.4 Differential Diagnosis

Disorders associated with ATM include a range of systemic autoimmune conditions such as systemic lupus erythematous, mixed connective tissue disorder, and Sjögren syndrome; other demyelinating conditions such as acute disseminated encephalomyelitis (ADEM), multiple sclerosis, and neuromyelitis optica (NMO); and a variety of tumors, injuries, and other anatomic problems that can cause spinal cord compression or impairment. Ischemic blood flow to the spinal cord, with or without infarction, can also present similarly to ATM. Despite efforts to identify a specific cause of ATM, the majority of cases are ultimately placed in the "idiopathic" category, meaning quite simply that no underlying cause was identified. Infectious and noninfectious conditions that should be considered in the differential diagnosis of ATM are listed in Box 21.2.

**Box 21.2 Approach to diagnosis of acute flaccid paralysis**

Physical examination including a detailed neurological evaluation

Laboratory testing:

- Serology for *Borrelia burgdorferi*, *Bartonella henselae*, Epstein-Barr virus, West Nile virus, human immunodeficiency virus
- CK levels, sedimentation rate, C-reactive protein
- Anti-DNA antibodies

Cerebrospinal fluid evaluation:

- Cell count with differential, protein, and glucose concentrations
- Bacterial culture and Gram stain
- PCR for polio and non-polio enteroviruses, VZV, EBV, HSV-1 and HSV-2, Powassan, Eastern equine encephalitis (EEE), Western equine encephalitis (WEE), St Louis encephalitis, California serogroup viruses, Herpes simplex 1 and 2, Epstein-Barr virus, human herpes virus 6, Cache Valley and California serogroup viruses
- Stool and nasopharyngeal specimens for polio and non-polio viral cultures
- Serum toxin and stool testing for botulism
- Electrodiagnostic studies
- Spinal or brain MRI depending on the location of symptoms

**Case Study**

### Practical Examples

**Case 1**

A 1-year-old previously healthy boy was hospitalized with arm weakness. Four days prior to admission, he developed fever, runny nose, cough, and decreased appetite. Two days prior to hospitalization, he was unable to use his left arm while drinking from his bottle. His mother noted a papular rash over the anterior mid-chest, neck, and hairline. His arm and hand weakness persisted, so he was hospitalized for further evaluation. His physical examination was consistent with acute flaccid paralysis, including left upper extremity weakness, decreased muscle tone, and an absent biceps reflex. MRI studies of the brain and spinal cord performed with gadolinium contrast were normal. Electromyography results were consistent with anterior motor horn dysfunction. Evaluation of the CSF revealed a mononuclear cell pleocytosis, with normal protein and glucose concentrations, and was positive for varicella-zoster virus DNA by polymerase chain reaction. The patient was diagnosed with VZV-associated *acute flaccid myelitis*. While prognosis for this illness is generally favorable, he did not recover muscle strength in his left arm.

**Case 2**

A 15-year-old male presented with a 3-week history of worsening paresthesias, associated with numbness and weakness in both lower extremities. On physical examination, he had marked urinary retention with decreased strength and muscle tone in both lower extremities. Evaluation of his CSF revealed a mononuclear cell pleocytosis with normal glucose and elevated total protein. MRI of the brain and spine cord performed with gadolinium contrast revealed an extensive lesion with patchy enhancement spanning from T4 to the L2, involving the cross section of the cord. An extensive diagnostic evaluation including studies for possible infectious, post-infectious, and autoimmune triggers did not reveal an underlying cause. The patient was diagnosed with idiopathic *acute transverse myelitis.* He was treated with systemic glucocorticoids, and his condition slowly improved.

## 21.5 Exercises

Please refer to the supplementary information section for answers to these exercises.

**Select the Single Best Response for each of the Following Questions:**

1. The most common cause of AFP in children is:
   A. Poliomyelitis
   B. Guillain-Barré syndrome
   C. Botulism
   D. West Nile virus

2. Acute manifestation of transverse myelitis includes all of the following *EXCEPT*:
   A. Acute progressive paresis
   B. Sensory deficit
   C. Loss of bowel and bladder function
   D. Spasticity

3. The cause of the cluster of acute flaccid myelitis (polio-like illness) in the United States during 2014 is:
   A. Poliovirus
   B. West Nile virus
   C. Enterovirus D68
   D. Unknown

## 21.6 Summary

Acute myelopathies are rare conditions that affect children of all ages. When they occur, they are frightening, and implementation of the available, optimal treatments requires a timely and accurate diagnosis. Performing a complete neurologic examination in children can be challenging, but its results are key to guide the initial diagnostic evaluation. A pediatric neurologist should be involved in the care of all individuals with acute onset of weakness. Treatment and prognosis depend on the underlying cause. The prognosis ranges from complete recovery to permanent paralysis or death.

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# Aseptic Meningitis

## Fever, Headache and A Stiff Neck…Not Looking So Sick

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**Learning Objectives**

- Recognize when a patient presents with a clinical syndrome consistent with aseptic meningitis
- Generate a differential diagnosis for aseptic meningitis
- Construct a plan to evaluate a patient presenting with aseptic meningitis

## 22.1 Introduction to the Problem

The approach to any patient with meningitis, regardless of the etiology, hinges on history, clinical assessment, and diagnostic testing, including results obtained directly from studying the cellularity and biochemistry of cerebrospinal fluid obtained by lumbar puncture. With the introduction of routine vaccinations against pyogenic bacteria that cause meningitis, the incidence of bacterial meningitis has decreased substantially, causing the relative proportion of aseptic meningitis cases to increase. Since many of the agents that cause aseptic meningitis are not reportable to public health authorities, the precise incidence of aseptic meningitis is not known. It is estimated, however, that tens of thousands of cases of aseptic meningitis occur in the United States each year [1].

There is significant clinical overlap among presentations of aseptic meningitis, bacterial meningitis, and meningoencephalitis. In rare cases, coinfection with a virus and a bacterium or a bacterium and a parasite can occur [2].

## 22.2 Definitions

**Aseptic meningitis** - Inflammation of the meninges, evidenced by pleocytosis in the cerebrospinal fluid, without the presence of an identifiable pyogenic bacterial pathogen (Table 22.1). For children and adults older than 3 months of age, pleocytosis is defined as six or more nucleated cells/mm$^3$. Neonates 28 days old or younger and neonates 28–56 days old require the presence of more than 19 and more than 9 nucleated cells/mm$^3$ respectively to meet the definition of cerebrospinal fluid pleocytosis [3]. In the absence of available rapid diagnostic tests (e.g., polymerase chain reaction (PCR) or rapid antigen testing), a useful surrogate for the diagnosis of "aseptic meningitis" during the initial evaluation stages can be a cerebrospinal fluid Gram stain that shows the presence of leukocytes without bacteria. However, such a Gram stain does not exclude all bacterial or fungal etiologies.

**Meningismus** - Also called meningism. Physical examination findings indicating meningeal inflammation, typically elicited by the examiner during maneuvers that stretch the meninges. These findings may be described as nuchal rigidity or a positive Kernig's and/or Brudzinski's sign. Nuchal rigidity is the absence of passive range of motion of the neck. Kernig's sign is indicated by pain elicited upon extension of the knee after hip flexion to 90 degrees. Brudzinski's sign is positive if the patient involuntarily lifts the legs upon passive flexion of the head and neck.

**Meningoencephalitis** - Inflammation of both the meninges and brain parenchyma. The latter is clinically evident by drowsiness, seizures, or altered mental status.

## 22.3 Basic Concepts

As is always the case, a thorough history and physical examination of the patient can lead to important diagnostic clues to explain their complaints. For patients suspected to have meningitis, elements such as antecedent illnesses and any associated medical treatments, the onset and evolution of symptoms, and epidemiologic risk factors can aid in generating a differential diagnosis. Family history should elucidate any risks for immunodeficiency, neoplasm, or uncommon inflammatory, autoimmune, or other rheumatologic conditions.

Typical presenting symptoms of meningitis include headache and meningismus. Other signs may include vomiting, lethargy, and anorexia. Fever is often but not always present. In preverbal infants and children, headache and meningismus may present as irritability or sharp high-pitched crying. Patients who are verbal may report photophobia, malaise, and decreased appetite. Seizures may be a presenting sign and should raise concern for a process involving the brain parenchyma. However, seizures themselves do not necessarily indicate the presence of a central nervous system infection. Some young children are prone to benign febrile seizures, and patients with underlying seizure disorders often experience lower seizure thresholds during times of stress, as occur during acute infections, particularly when associated with fever. On the other hand, a diminished level of consciousness, drowsiness, confusion, or obtundation should elevate concern for the presence of a pathologic central nervous system process, including infection.

> The possibility of suppurative bacterial meningitis should be considered in any patient who presents clinically with suspected aseptic meningitis.

A priority in the evaluation of suspected aseptic meningitis includes an evaluation for the possibility that the patient has the more serious infection, suppurative bacterial meningitis. Bacterial meningitis can be fatal if not identified and treated in a timely fashion. The initial evaluation for possible bacterial meningitis includes a lumbar puncture to collect cerebrospinal fluid (CSF). The CSF is submitted to the clinical laboratory with requests for cellular and biochemical analysis, Gram stain, and bacterial culture. Prompt administration of broad spectrum antibiotics that reach the central nervous system is essential. Adjunctive therapy with systemic glucocorticoids is initiated when indicated.

A lumbar puncture for CSF evaluation should also be performed to evaluate patients with suspected aseptic meningitis. CSF cell count and differential, total glucose, total protein, Gram stain, and bacterial culture are all still recommended as the results can lead to important clues regarding the etiology of the infection. Diagnostic testing for the presence of enteroviral or herpes simplex virus nucleic acid

**Table 22.1** Patterns of cerebrospinal fluid analysis findings typically found in patients with meningitis caused by different groups of pathogens

| | Total number of nucleated cells | Differential | Glucose | Protein |
|---|---|---|---|---|
| Normal | Age 0–28 days: 0–19/mm$^3$<br>Age 29–56 days: 0–9/mm$^3$<br>Age over 56 days, adults: 0–5/mm$^3$ | Absence of or very few neutrophils | More than 60% of serum glucose | Normal |
| **Pathogen group** | **Total number of nucleated cells** | **Differential** | **Glucose** | **Protein** |
| Viruses | Up to 1000/mm$^3$ | Lymphocyte predominance | More than 60% of serum glucose | Elevated |
| Pyogenic bacteria | Markedly elevated, usually over 500/mm$^3$ | Neutrophil predominance | Less than 40% of serum glucose, may be undetectable | Elevated |
| Lyme disease | Elevated, usually 100–500/mm$^3$ | Lymphocyte predominance | More than 60% of serum glucose | Normal or slightly elevated |
| Tuberculosis | Elevated, usually up to 500/mm$^3$ | Mononuclear cell (monocyte and lymphocyte) predominance | Less than 40% of serum glucose | Elevated |
| Fungal | Elevated, usually 100–500/mm$^3$ | Mononuclear cell (monocyte and lymphocyte) predominance | Less than 40% of serum glucose | Elevated |
| Parasitic | Elevated, usually 100–500/mm$^3$ | Increased eosinophils | Less than 40% of serum glucose | Elevated |

should be considered. A peripheral blood sample should be submitted to the laboratory for Lyme disease serologies if the patient lives in or has traveled to a Lyme endemic area. When the medical history and/or physical examination reveal clues that the infection may be caused by other agents, additional pathogen-specific serologic tests or PCR-based tests on CSF can be requested.

In patients who are deemed at high risk for uncal herniation, a computed tomographic scan of the brain should be performed prior to lumbar puncture. National guidelines in the United Kingdom recommend neuroimaging prior to lumbar puncture for children who are immunocompromised and for those with focal neurologic deficits, papilledema, unstable seizures, relative bradycardia with hypertension, abnormal vestibulo-ocular (doll's eyes) reflex, or a Glasgow Coma Score less than 13 [4]. National guidelines in the United States recommend that adults undergo computed tomography scanning of the brain prior to lumbar puncture if they are immunocompromised; have a history of central nervous system disease, including stroke; or have developed new onset seizures, papilledema, altered mental status, or a focal neurologic deficit on physical examination [5]. In all cases, lumbar puncture is contraindicated if the patient is at high risk for bleeding or if there is an active bacterial infection at the site where the lumbar puncture would otherwise be performed.

An opening pressure should be obtained when performing a lumbar puncture. A sufficient volume of cerebrospinal fluid is then collected to submit to the clinical laboratory for diagnostic testing. When possible, additional fluid should be obtained and held for studies that may need to be added based on clues provided with the first round of results. General laboratory studies that should be sent on cerebrospinal fluid include total cell count and differential, total protein and glucose, Gram stain, and bacterial culture. For an accurate interpretation of the result of the CSF glucose concentration, a serum glucose should be requested in parallel. Targeted testing can also be sent to evaluate for infections caused by specific etiologic agents (Table 22.2).

## 22.4 Partially Treated Bacterial Meningitis

In some cases, patients may present for evaluation for suspected meningitis after having received prior antibiotic therapy. A determination of whether the patient's illness represents bacterial meningitis can be made using several points of information. CSF indices may still be suggestive of bacterial meningitis, although the Gram stain and culture may fail to reveal bacteria because of the limited antibiotics they have already received (Table 22.1). The clinical history and determination of risk can identify conditions which predispose to bacterial meningitis such as immunodeficiency, antecedent infection, and, for children, not being current on standard recommended immunizations. In some circumstances, bacteria may be seen on Gram stain but fail to grow

**Table 22.2** Typical laboratory tests performed on cerebrospinal fluid during the diagnostic evaluation for meningeal infection

| Laboratory test | Circumstances where results are most likely to be helpful |
|---|---|
| Total cell count and differential | All cases of suspected meningitis |
| Total glucose and protein | All cases of suspected meningitis |
| Gram stain | All cases of suspected meningitis |
| Bacterial culture | All cases of suspected meningitis |
| Mycobacterial culture | Very low yield. May be useful in the diagnostic evaluation for tuberculous meningitis if a large volume of CSF can be collected for centrifugation with culture performed on the pellet |
| Acid fast stain | Very low yield. May be useful in the diagnostic evaluation for tuberculous meningitis if a large volume of CSF can be collected for centrifugation with acid fast staining performed on the pellet |
| PCR-based testing for enterovirus | All cases of suspected aseptic meningitis. Higher yield during summer months |
| PCR-based testing for human parechovirus | Useful if a viral entity is suspected, but other viral studies are negative<br>Should be considered with a clinical picture consistent with meningitis or meningoencephalitis without a significant CSF pleocytosis |
| PCR-based testing for herpes simplex viruses | Newborns; all cases of suspected aseptic meningitis; a very important test in the diagnostic evaluation of meningoencephalitis |
| PCR-based testing for bacterial 16 s rRNA | May be useful if partially treated bacterial meningitis is suspected |
| PCR-based testing for *Borrelia burgdorferi* | Not standardized. Instead, two-tiered serologic testing should be done from a peripheral blood sample in cases of suspected Lyme meningitis |
| *Cryptococcus* antigen assay | Immunocompromised host, especially advanced human immunodeficiency virus infection; exposure to bird droppings |
| Venereal disease research laboratory (VDRL) | Suspected central nervous system syphilis |
| West Nile virus-specific IgM | The preferred test to document West Nile virus neuroinvasive disease. A serum IgM test can be performed at the same time |

in culture. Other adjunctive laboratory studies have been used with mixed results. Rapid bacterial antigen tests have not been shown to be superior to Gram stain alone in one series [6] and are generally lacking in sensitivity and specificity. Newer technologies include nucleic acid-based testing, including a rapid (1 h) multiplex PCR and 16s rRNA sequencing. The utility of these tests depends on local availability and timeliness of the results.

## 22.5 Enteroviruses: The Leading Cause of Aseptic Meningitis

Enteroviruses are the most common cause of aseptic meningitis.

The non-polio enteroviruses cause the majority of cases of aseptic meningitis in the modern era [7]. Enteroviruses are a diverse group of RNA viruses with varying geographic distribution. Over 100 strains have been identified and include echoviruses, coxsackieviruses A and B, and the numerically identified enteroviruses (e.g., enterovirus D68) (Fig. 22.1). Some members of this large group, such as enterovirus 71, tend to cause more severe neurologic manifestations including rhombencephalitis with seizures and a polio-like acute ascending paralysis.

As a group, enteroviruses circulate with a seasonal pattern. In temperate climates, enteroviruses cause more frequent illness and outbreaks during the summer and fall but tend to circulate year-round in the tropics. Enteroviruses are typically spread through the fecal-oral route or through direct contact with secretions or fomites that are contaminated with stool or respiratory secretions. Enteroviruses are alcohol-stable since the virions are nonenveloped. Hand washing with soap and water is recommended to prevent transmission.

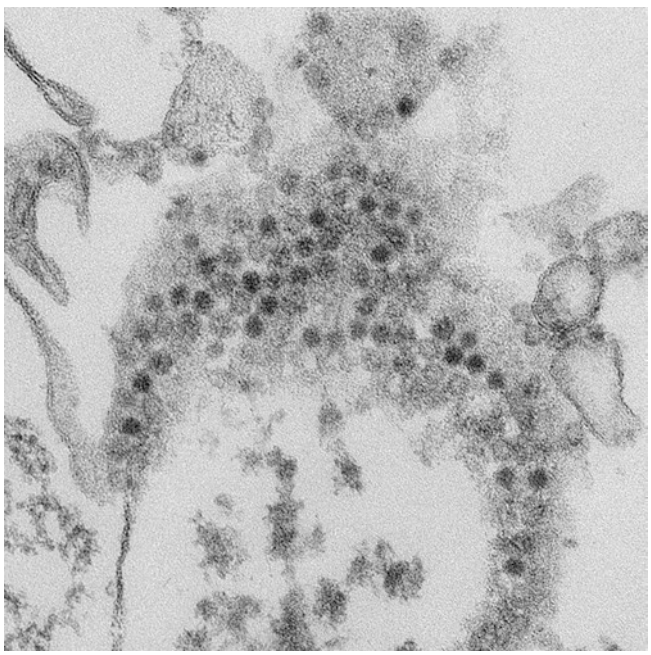

**Fig. 22.1** Scanning electron micrograph of enterovirus D68. (Image Credit: CDC/Cynthia S. Goldsmith, Yiting Zhang)

Parechovirus infection may present with a clinical presentation concerning for aseptic meningitis, but with little or no CSF pleocytosis.

Parechoviruses were formerly classified as enteroviruses but have now been reclassified separately. Patients infected with parechovirus may present with encephalitis or aseptic meningitis. Central nervous system infection from parechoviruses may not lead to a CSF pleocytosis despite clinical findings consistent with neurologic involvement.

The typical case of aseptic meningitis caused by an enterovirus is a patient with a subacute onset of headache and meningismus. The patient may be uncomfortable or mildly ill-appearing but does not appear toxic. The history may reveal a mild preceding respiratory infection or a history of close contact with another individual experiencing a mild to moderate respiratory or gastrointestinal disease.

The CSF profile will show pleocytosis (as noted, aseptic meningitis secondary to parechovirus infection does not always do so), with a predominance of mononuclear cells. CSF protein is elevated, and the glucose is normal. Gram stain will reveal leukocytes but no bacteria. Diagnostic testing for enteroviruses can also be performed on CSF using PCR. PCR-based tests are most sensitive if performed on CSF collected within the first 2 days of symptoms [8]. Most, but not all, enteroviruses grow very well in standard cell lines still used in some clinical microbiology laboratories but only very rarely will grow from CSF. When cultures are obtained from patients with aseptic meningitis, enteroviruses are much more likely to be recovered from samples collected from the respiratory and/or gastrointestinal tract than they are from the CSF.

Antiviral therapy is not currently available for the treatment of aseptic meningitis caused by enteroviruses; treatment is supportive. In neonates with sepsis caused by enteroviruses, some clinicians will administer pooled human immunoglobulin intravenously. Several investigational antiviral agents have been assessed for the treatment of severe enterovirus infection, but none are currently available.

## 22.6 Herpes Simplex Viruses

A primary central nervous system infection caused by herpes simplex virus (HSV) 1 or 2 can lead to a severe, life-threatening destructive meningoencephalitis. The clinical presentation is abrupt with clear evidence of involvement of the brain parenchyma. Neonates are particularly vulnerable to severe disease. Extensive guidance on evaluation of neonates potentially exposed to, or infected with, HSV has been published [10]. In contrast, primary disease in adolescence and adults, and reactivation of a prior infection of the mucous membranes, can cause aseptic meningitis, a milder albeit very uncomfortable illness. In adults, HSV-associated aseptic meningitis cases peak during the 4th decade of life [9]. Recurrent HSV meningitis can occur with virus reactivation.

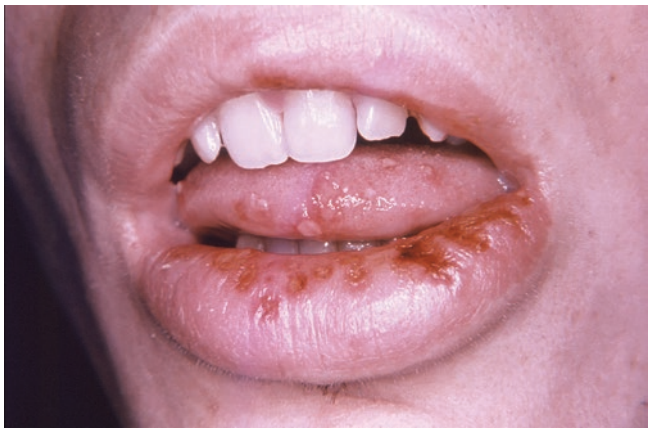

**Fig. 22.2** Primary herpes simplex virus gingivostomatitis with vesicles and ulcers of the oral mucosa and lips. (Photo Credit: CDC/ Robert E. Sumpter)

The diagnosis of HSV aseptic meningitis is confirmed by testing for the presence of HSV-specific nucleic acid in the patients' CSF using PCR. Viral cultures performed on CSF have very low yields but can be useful when collected from suspicious lesions found on the patient's mucous membranes. Physical examination may reveal a vesicular or ulcerative rash on the genitals, in the oropharynx, or at other sites if there is primary infection (Fig. 22.2), but reactivation disease often occurs without a rash. Vesicles can be unroofed and tested to confirm HSV infection using a direct fluorescence antibody technique, viral culture, or PCR.

Antiviral treatment of central nervous system HSV infection is available in the form of intravenous acyclovir. After a treatment regimen has been completed for primary HSV disease, suppressive therapy using oral acyclovir or one of its derivatives (e.g., valacyclovir) can be considered in an effort to prevent reactivation. This strategy is quite effective at suppressing oral or genital disease and to reducing mucosal shedding; however it has not been shown to reduce episodes of recurrent HSV meningitis [11].

## 22.7 *Borrelia burgdorferi*: The Bacterial Cause of Lyme Meningitis

Lyme disease is caused by the spirochete *Borrelia burgdorferi*. Aseptic meningitis is one of the classic presentations seen during the early disseminated stage of infection (see ▶ Chap. 32). *B. burgdorferi* is transmitted in the United States by deer ticks, *Ixodes scapularis* and *Ixodes pacificus*. In Europe, *Ixodes ricinus* is known to transmit borreliosis. In the early localized stage of infection, the pathognomonic rash of erythema chronicum migrans may be present (Fig. 22.3). If early localized infection goes unrecognized or untreated, the patient can develop early disseminated infection. Neurologic manifestations can include aseptic meningitis; cranial nerve palsies, especially involving the facial nerve; or radiculopathy.

In the United States, Lyme endemic areas include the mid-Atlantic states north through New England and the

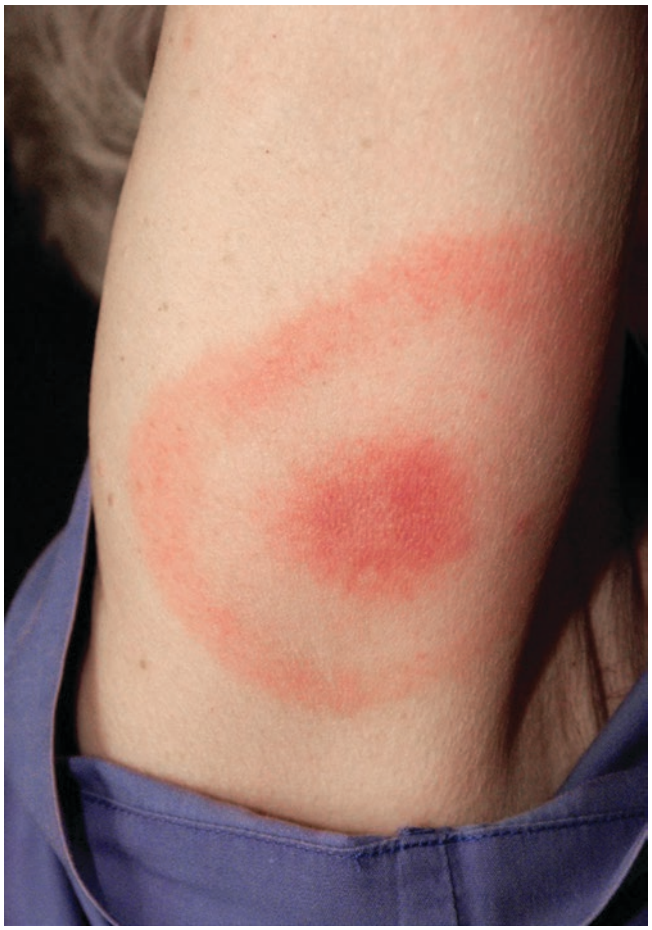

**Fig. 22.3** Erythema chronicum migrans rash of early localized Lyme infection. (Photo Credit: CDC/James Gathany)

upper Midwest (Minnesota and Wisconsin) (Fig. 22.4). More than 95% of cases of Lyme disease are reported from these areas. In Canada, Lyme disease occurs along much of the southern border with the United States. The vast majority of cases are reported in Ontario, Nova Scotia, and Québec.

Combining elements of the medical history, the clinical presentation, and results of laboratory tests is necessary for a diagnosis of Lyme meningitis. The patient should have a compatible epidemiologic exposure and a clinical presentation that is consistent with Lyme disease. Two-tier serologic testing is necessary. The first tier involves performing an enzyme-linked immunoassay (EIA) that screens for the presence of any antibodies directed against *B. burgdorferi*. If the EIA result is equivocal or positive, confirmatory testing is performed using the western blot technique. The western blot technique identifies the specific *B. burgdorferi* antigens that are recognized by the IgM or IgG antibodies present in the patient serum. The number and types of antibodies that are detected are used to interpret the result of the test. Like all antibody tests, results remain positive even after successful treatment. The cerebrospinal fluid examination of patients with Lyme meningitis will show pleocytosis with a predominance of lymphocytes. A positive Lyme PCR on CSF supports the diagnosis of Lyme meningitis, but serologic testing performed on serum collected from peripheral blood is the gold standard used to diagnose Lyme disease during the early disseminated and late stages of infection. Recommended treatment for Lyme meningitis is with oral doxycycline or intravenous ceftriaxone for 14 days [12, 13]. Clinical improvement in response to treatment with antibiotics is usually obvious within a few days. The antibiotic regimen cures the infection. Long-term prognosis is excellent.

## 22.8 Arboviruses as Etiologies for Aseptic Meningitis

The term "arboviruses" does not describe a formal taxonomic family or genus of viruses but is used instead to describe a large, mixed group of viruses that are **ar**thropod-**bo**rne. Arthropods are invertebrates with an exoskeleton, a segmented body, and paired joint appendages. Mosquitos, ticks, and sandflies are the three groups of arthropods known to transmit arboviral infections to humans. In general, arboviruses cause systemic infections with potential to involve multiple tissues, including those of the brain and spinal cord. Most arboviral infections of the central nervous system involve both the meninges and the brain parenchyma leading to the clinical problem of meningoencephalitis as seen with infections caused by Powassan, a tick-borne arbovirus, and St. Louis encephalitis virus, a mosquito-borne pathogen. Isolated involvement of the meninges is less typical for arbovirus infection, although the mosquito-borne West Nile virus can cause a full spectrum of neuroinvasive disease that ranges from aseptic meningitis to encephalomyelitis and meningoencephalitis. All arboviruses have a zoonotic cycle and may appear in intermediate animal hosts prior to being recognized as the cause of human disease outbreaks. A definitive diagnosis of central nervous system arbovirus infection can be made by detecting pathogen-specific antibodies in the cerebrospinal fluid or serum. Antibody-based testing has proved especially important in the diagnosis of West Nile neuroinvasive disease because of the unexpected, very poor sensitivity of PCR-based tests for this infection. PCR-based tests are quite sensitive and available and for the diagnosis of infections caused by other arboviruses. The treatment for arbovirus-related neurological disease is supportive.

## 22.9 Less Common Causes of Aseptic Meningitis

Other causes of aseptic meningitis are listed in Tables 22.3 and 22.4. There are also several noninfectious causes of aseptic meningitis. If the medical history reveals that a medication was newly introduced or that the patient had recently received an immunoglobulin infusion, these treatments should be considered as a potential noninfectious cause of aseptic meningitis. Rare genetic conditions can also cause aseptic meningitis that is not associated with an infection.

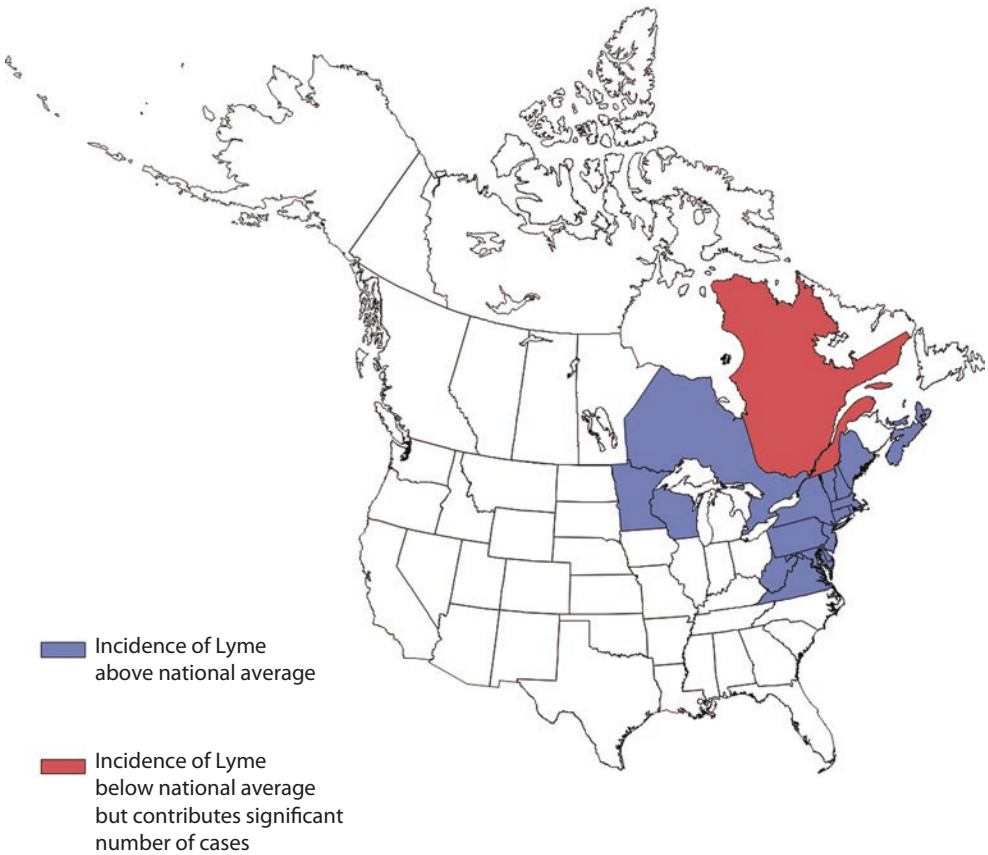


**Fig. 22.4** Geographic distribution of Lyme disease in the United States and Canada. (Data sources: The United States Centers for Disease Control and Prevention, Government of Canada)

**Table 22.3** Etiologies of aseptic meningitis

| **Infectious etiologies** | | |
|---|---|---|
| **More common** | **Less common** | **Rare** |
| Partially treated suppurative bacterial meningitis<br>Enteroviruses<br>Herpes simplex viruses<br>*Borrelia burgdorferi*<br>Human parechovirus<br>West Nile virus | Adenoviruses<br>Epstein-Barr virus<br>Cytomegalovirus<br>Varicella zoster virus<br>JC virus<br>St. Louis encephalitis virus<br>Powassan virus<br>Human immunodeficiency virus<br>*Bartonella henselae* | Mumps virus<br>Polio viruses<br>Lymphocytic choriomeningitis virus<br>Dengue viruses |
| **Noninfectious etiologies** | | |
| Drug induced: Immunoglobulin intravenous | Paraneoplastic syndromes<br>Drug induced: Sulfasalazine Amoxicillin Trimethoprim plus sulfamethoxazole Postvaccination | Cryopyrin-associated periodic fever syndromes<br>Kikuchi's disease |

**Table 22.4** Epidemiologic risk factors for certain causes of aseptic meningitis

| Cause | Epidemiologic risk factor(s) |
|---|---|
| Eastern equine encephalitis | Exposure to mosquitos in specific isolated swampy areas of Florida and upstate New York |
| Western equine encephalitis | Few or no cases reported in recent years, once fairly restricted to the western United States |
| Venezuelan equine encephalitis | Exposure to mosquitos in central and South America, particularly southern parts of Mexico, Bolivia, Colombia, Ecuador, Peru, and Venezuela |
| Japanese encephalitis virus | Prolonged residence or travel to rural areas of the western Pacific and Indian subcontinent. Summer and fall in temperate areas, year-round in tropical areas. Largely vaccine preventable |
| Dengue viruses 1, 2, 3, and 4 | Exposure to mosquitos in most tropical areas of the world |
| *Borrelia burgdorferi* | Exposure to *Ixodes* species ticks in endemic areas |
| Lymphocytic choriomeningitis virus | Exposure to wild or pet rodents or their urine |

Kikuchi-Fujimoto disease, or necrotizing histiocytic lymphadenitis, is characterized by lymphadenopathy, fever, and leukopenia. Aseptic meningitis may also be present in this self-limited disease. Anti-NMDA receptor encephalitis may initially present as aseptic meningitis before progression of symptoms to include encephalitis. Aseptic meningitis may also be seen in association with a paraneoplastic syndrome.

Uncommon infections should also be considered in ill patients with CSF findings of inflammation that are atypical for suppurative bacterial meningitis. Fungal meningitis should be included in the differential diagnosis of meningitis in immunocompromised, those with recent head trauma associated with skull fractures with or without obvious CSF leaks, or through accidental, iatrogenic direct inoculation from a medication contaminated with a mold. Cryptococcus meningitis occurs with compatible risk factors but is most closely associated with disease among patients with very poorly controlled infection with human immunodeficiency virus. A cryptococcal antigen test performed on CSF provides a rapid diagnosis. The use of CSF India ink preparations for the diagnosis of cryptococcal meningitis has fallen and has largely been replaced by the more sensitive antigen-based testing methods.

Viral causes of aseptic meningitis not previously discussed include human immune deficiency virus, mumps, poliomyelitis, and various zoonotic viruses. Acute infection with human immune deficiency virus causes aseptic meningitis in up to 17% of newly infected patients [14]. Aseptic meningitis is a very uncommon, but well recognized, side effect of vaccination with live attenuated mumps vaccine. Natural mumps infection was once a very common cause of aseptic meningitis but, following the introduction of and widespread use of mumps vaccine, is quite rare. Similarly, aseptic meningitis was once a fairly common manifestation of poliovirus infection, but successful immunization programs have made wild poliovirus infections so rare that global eradication may soon be achieved. Zoonotic viruses, such as lymphocytic choriomeningitis virus and Seoul virus, can spread among commercial breeding colonies of rodents and inadvertently infect humans who have direct contact with the animals or their urine.

Large volumes of cerebrospinal fluid may be needed to isolate *Mycobacterium tuberculosis* in culture.

Some bacterial causes of meningitis lead to CSF findings that appear more consistent with aseptic meningitis than suppurative bacterial disease. These agents are not seen on standard Gram stain and do not grow in the laboratory when routing bacteriologic methods are used. *Borrelia burgdorferi*, the bacterial cause of Lyme meningitis, has been discussed in detail already. Other examples include *Mycobacterium tuberculosis* and *Bartonella henselae*. Tuberculous meningitis can occur in any setting but is most common among children less than 5 years of age who live in high prevalence areas. Tuberculous meningitis has an indolent presentation with worsening malaise, fever, and personality change. As the infection advances, cranial nerve palsies and long tract signs such as spasticity and hyperreflexia develop. The illness is associated with substantial mortality, usually secondary to increased intracranial pressure leading to brainstem herniation. Only the early, nonspecific indolent signs and symptoms would be mistaken for aseptic meningitis. The diagnosis of tuberculous meningitis is made by recovering *M. tuberculosis* from CSF culture or by identifying the presence of the organism using PCR-based techniques. Large volumes of CSF (10 ml or more) may be needed to adequately identify the organism in culture. The diagnosis is suggested by the presence of a mononuclear cell predominance in the CSF together with an elevated total protein and very depressed total glucose concentration (sometimes undetectable). Treatment requires a prolonged course of anti-tuberculous therapy. Glucocorticoids are used adjunctively early during treatment to reduce central nervous system inflammation.

*Bartonella henselae*, the agent of cat scratch disease, typically causes meningoencephalitis when the central nervous system is involved, but aseptic meningitis has also been described. The CSF analysis reveals a pleocytosis with a predominance of mononuclear cells, a normal glucose, and normal or elevated protein concentration. The Gram stain shows leukocytes but no bacteria. The diagnosis is usually made serologically, but CSF PCR is also available.

## Case Study

### Practical Examples

**Example 1**

A 17-year-old girl presents with headache and fever for several days. She reports a new sexual partner and a painful sore on her labia majora. Her physical examination reveals meningismus and the presence of vesicles and small ulcers on her labia majora.

This case is illustrative of herpes simplex virus meningitis, likely associated with her primary genital infection. Due to her symptoms, the patient should undergo lumbar puncture to confirm the diagnosis. Treatment with a brief course of intravenous acyclovir will shorten her course of symptoms.

**Example 2**

A 40-year-old woman presents with 3 days of unrelenting headache and photophobia during the summer. Five days prior to the onset of her headache, she had a "stomach bug" with watery diarrhea. She now complains of unremitting headache only partly relieved after by acetaminophen. She appears uncomfortable and squints under the bright lights of the examination room. A lumbar puncture is performed. Laboratory analysis of her CSF shows 70 nucleated cells/mm$^3$ with 85% lymphocytes and 15% neutrophils. The CSF total protein concentration

is 30 mg/dl, and glucose concentration is 70 mg/dl.

Depending on where she has lived or traveled, her illness could be consistent with Lyme meningitis. The history of the antecedent "stomach bug" favors a diagnosis of enterovirus meningitis. Both illnesses are most common during the summer, and both lead to a patient who is relatively well-appearing. An enterovirus PCR should be obtained on CSF and Lyme serologies performed on serum. Treatment for enterovirus meningitis is supportive. Treatment of Lyme meningitis includes a 14-day course of doxycycline. It would not be unreasonable to initiate antibiotic treatment for possible Lyme disease while waiting for confirmatory test results.

**Example 3**

An 18-month-old boy presents to the emergency department with lethargy and fever. His parents report that he has been taking amoxicillin for a "kidney infection" for the past 2 days. His fever has been as high as 39 °C. Review of records shows that he has received vaccinations at 2 months and 4 months but did not keep appointments for further well-child visits. Exam reveals a lethargic boy being held by his mother. You note that he does not move or cry during phlebotomy or intravenous catheter placement. He opens his eyes briefly and lets out a high-pitched cry when you try, unsuccessfully, to flex his neck.

A lumbar puncture is performed. The cerebrospinal fluid has 120 nucleated cells/mm$^3$ with 80% neutrophils and 20% lymphocytes. The total protein is 60 mg/dl, and glucose is 40 mg/dl. A Gram stain shows no organisms but many polymorphonuclear leukocytes.

This presentation is consistent with partially treated, suppurative bacterial meningitis. With the history of prior receipt of amoxicillin, the CSF Gram stain and culture may be negative. The history of partial vaccination is also concerning, since the series of vaccines given as an infant protect against the three major causes of meningitis *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae* serotype B. This child should be given intravenous antibiotics, while further evaluation is underway.

## 22.10 Exercises

Please refer to the supplementary information section for answers to these exercises.

1. A 17-year-old girl presents with a diffuse headache and photophobia. The onset has been gradual over the last few days but is getting worse.
   - *What additional information would you like to know?*
   - *What laboratory studies would you like to obtain?*
   - *What is included in your differential diagnosis? How does this change if the patient is 3 months old?*

2. A lumbar puncture is performed. Initial results are below:
   - Nucleated cell count: 15 cells/mm$^3$, 75% lymphocytes, and 25% neutrophils. The CSF is described as clear, with no red blood cells noted.
   - Total protein 55 g/dl, glucose 60 g/dl
     - *Which diagnosis is more likely with these lab results? How would this be different if the patient were 3 weeks old? 6 weeks old?*
     - *How would your differential diagnosis change if the patient was a recent immigrant to the United States and the cell count showed 115 cells/mm3, with 90% monocytes?*

3. A Gram stain shows no organisms. Bacterial cultures reveal no growth.
   - *What additional tests would help diagnose the 17-year-old girl?*
   - *What tests would you order if the patient were an infant?*
   - *What tests would you order if the patient spent time outdoors and reported mosquito or tick bites?*
   - *What additional considerations would you have if the patient was infected with HIV?*

## 22.11 Summary

Aseptic meningitis is diagnosed when a patient who is mildly or moderately ill has a CSF pleocytosis with a mononuclear cell predominance and no identifiable suppurative bacterial cause on routine cultures. A thorough history of symptoms and epidemiologic risk factors is important to direct diagnostic testing. Potential etiologies differ based on the patient's age and potential or known exposures. While viruses account for the majority of cases of aseptic meningitis, there are numerous other infectious and noninfectious causes. Early disseminated infection with *Borrelia burgdorferi* accounts for a substantial number of cases of aseptic meningitis in Lyme disease endemic areas.

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# Bacterial Meningitis

## Fever, Headache and A Stiff Neck…Looking Pretty Sick

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**Learning Objectives**

- Recognize the typical clinical manifestations of bacterial meningitis in neonates, infants, children and adults.
- Outline the general approach to the diagnosis of bacterial meningitis.
- Discuss key management issues for patients with bacterial meningitis.
- Identify common acute complications and long-term sequelae of bacterial meningitis.
- Describe measures used to prevent bacterial meningitis.

## 23.1 Introduction

Bacterial meningitis is an acute inflammatory process due to infection of the leptomeninges (or meninges) surrounding the brain and spinal cord. The leptomeninges are composed of three layers: the pia mater, the arachnoid mater, and the dura mater. Bacterial meningitis is a life-threatening infection that requires prompt medical intervention and, even with proper treatment, is associated with significant morbidity and mortality. This chapter provides a framework for the clinical approach to patients with suspected bacterial meningitis based on their age, underlying risk factors, physical examination findings, and diagnostic laboratory test results. It is important to be aware of the epidemiology of the common etiologic pathogens and the usual empiric antibiotic treatment regimens based on the patient's age and underlying risk factors. Complications resulting from bacterial meningitis are relatively common and can occur at any time during the course of treatment. Unlike other infections that are commonly treated with intravenous antibiotics on an outpatient basis, therapy for bacterial meningitis is often completed in the hospital. A firm understanding of the complications that might occur during the acute phase of the infection facilitates their early recognition and management and may improve outcome. An appreciation of the more common long-term sequelae of bacterial meningitis is also important so that appropriate referrals and follow-up can be arranged prior to hospital discharge.

## 23.2 Definitions

**Bacterial meningitis** - inflammation of the meninges caused by a bacterial infection.

**Cerebrospinal fluid (CSF)** - the aqueous fluid that flows within the ventricles of the brain and the subarachnoid space enveloping and cushioning the brain and spinal cord.

**Lumbar puncture** - the procedure of advancing a hollow spinal needle into the subarachnoid space from the skin between the 3rd and 4th or 4th and 5th lumbar vertebrae, most typically to collect cerebrospinal fluid for diagnostic testing. Lumbar punctures are also performed to access the subarachnoid space for the direct administration of some medications.

**Meninges** - the three membranes surrounding the brain and spinal cord including the thick outer dura mater that is in direct contact with the skull, the delicate arachnoid mater positioned in between the dura mater and the pia mater, and the innermost pia mater that is in direct contact with the cerebral cortex and spinal cord. The pia mater is impermeable allowing it to enclose the cerebrospinal fluid in the subarachnoid space that separates the pia mater from the arachnoid mater.

**Meningitis** - inflammation of the membranes surrounding the brain and the spinal cord.

**Meningismus** - a clinical term used to describe the presence of nuchal rigidity (neck stiffness) and headache.

## 23.3 Basic Concepts

**Case Study**

**Practical Examples**

As you read each of these cases, consider the possible diagnoses and additional diagnostic studies that would facilitate clinical decision making:

**Case 1**

A 3-week-old female, born at full-term, is brought to the emergency department because of poor feeding and feeling cool to the touch. Her physical examination shows an irritable infant with a full anterior fontanelle. Her rectal temperature is 36 °C (96.8 °F), heart rate is 180 beats per min, respiratory rate is 60 breaths/min, and blood pressure is 86/52 mm Hg.

**Possible diagnoses (the differential diagnosis list):**

_____
_____
_____

**Additional diagnostic studies:**

_____
_____
_____

**Case 2**

A 10-year-old boy presents to the emergency department with a 3-day history of headache, nasal congestion, and fever. Today, he developed swelling and redness around his right eye. He has been otherwise healthy and has received all age-appropriate immunizations.

On physical examination, he is difficult to arouse. His temperature is 38.6 °C, heart rate is 120 beats/min, respiratory rate is 20 breaths/min, and blood pressure is 116/80 mm Hg. He has proptosis (bulging of the eye anteriorly) with marked redness, swelling, and tenderness around his right eye. He is unable to cooperate with an assessment of his extraocular movements. He resists neck flexion.

**Possible diagnoses (the differential diagnosis list):**

_____
_____
_____

**Additional diagnostic studies:**

_____
_____
_____

**Case 3**

A 20-year-old man presents to the office with a 4-h history of fever, chills, and vomiting. He "aches all over," including a "bad headache." He is previously healthy and has received all age-appropriate vaccinations, including a seasonal influenza vaccine and two doses of the quadrivalent meningococcal conjugate ACWY vaccine at ages 12 and 18 years.

On physical examination, the man appears quite ill. He is drowsy but answers questions appropriately. He asks for the room lights to be turned off stating that the bright lights make his headache worse. His vital signs show a temperature of 39 °C, heart rate of 120 beats/min, and blood pressure of 100/72 mm Hg. His mucus membranes are dry. On auscultation of his heart, his tachycardia has a regular rhythm. A grade II/VI systolic murmur is appreciated along the left lower sternal border. His lung and abdominal examinations are normal. Pinpoint red and dark purple macules that do not blanch with pressure are noted on his feet and lower legs.

**Possible diagnoses (the differential diagnosis list):**

_____

_____

_____

**Additional diagnostic studies:**

_____

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## 23.3.1 Epidemiology and Microbiologic Causes of Bacterial Meningitis

The common microbiologic causes of bacterial meningitis vary depending on the patient's age (Table 23.1). The incidence of bacterial meningitis also varies according to age with the highest rates documented among children under 2 months (80.7 cases per 100,000 population) [1], an observation primarily due to risk factors unique to newborns (Table 23.2). During the newborn period, *Streptococcus agalactiae* (group B streptococcus) accounts for up to 60% of all cases of bacterial meningitis [2]. Fortunately, screening for maternal colonization with *S. agalactiae* during pregnancy has become a standard of care. Women known to be colonized at any time during their pregnancy are treated with intrapartum intravenous antibiotics, an intervention that has successfully reduced early-onset (occurring during the first week of life) group B streptococcal disease, by 86%. Unfortunately, this strategy has not reduced observed rates of late-onset (occurring between 1 week and 3 months of age) group B streptococcal infection [2]. *E. coli* is the most frequent aerobic gram-negative bacillus to cause bacterial meningitis in the newborn. Factors known to increase the risk for infection with this pathogen include prematurity, very low birth weight, traumatic delivery, myelomeningocele, congenital anomalies of the genitourinary tract, and galactosemia, a rare genetic metabolic disorder of galactose metabolism [3]. Other aerobic gram-negative bacilli associated with neonatal meningitis include *Citrobacter koseri* and *Enterobacter* species. Both of these organisms offer added challenges because of their proclivity to cause brain abscesses and their tendency to be resistant to multiple classes of antibiotics [4, 5]. Neonatal meningitis caused by the gram-positive bacillus *Listeria monocytogenes*, once seen on a fairly regular basis, is now quite rare.

The most common causes of bacterial meningitis in previously healthy, fully immunized infants and older children are *Streptococcus pneumoniae* and *Neisseria meningitidis* [6]. Infections with gram-negative bacilli are unusual in this age group; however unimmunized children less than 5 years of age again are at risk for invasive infection secondary to *Haemophilus influenzae* type b (Hib).

**Table 23.1** Typical causes of bacterial meningitis by age

| Age | Bacteria |
|---|---|
| Less than 1 month (newborn) | *Streptococcus agalactiae* (group B streptococcus)<br>*Escherichia coli*<br>Other aerobic gram-negative bacilli including *Citrobacter koseri*<br>*Listeria monocytogenes* |
| 1–3 months | *S. agalactiae* (group B streptococcus)<br>*Streptococcus pneumoniae*<br>*Neisseria meningitidis*<br>*Haemophilus influenzae* type b |
| 3 months to 5 years | *Streptococcus pneumoniae*<br>*Neisseria meningitidis*<br>*Haemophilus influenzae* type b (incompletely immunized) |
| 6–17 years and young adults | *S. pneumoniae*<br>*N. meningitidis* |
| Older adults | *S. pneumoniae*<br>*N. meningitidis*<br>*Listeria monocytogenes* |

Prior to the development and widespread use of conjugate *Haemophilus influenzae* type b (Hib) vaccine in the late 1980s, Hib was responsible for causing approximately 10,000 cases of bacterial meningitis each year in children less than 5 years of age in the USA alone. It was, by far, the most common cause of bacterial meningitis in young children. Hib vaccine first became available in the late 1980s. With widespread uptake during the early 1990s, the incidence of Hib meningitis in young children dropped by 95%, while the incidence of all cause bacterial meningitis decreased by 55% [7]. Worldwide, rates of childhood Hib meningitis have decreased in every region where the vaccine has been introduced.

In the USA, the introduction of pneumococcal conjugate vaccine (PCV7) in 2000 led to a further 69% decrease in the incidence of bacterial meningitis among US children younger than 2 years of age [8]. As the substantial benefits of the vaccine program were being realized, emergence of invasive pneumo-

**Table 23.2** Risk factors for bacterial meningitis in newborns (age less than 1 month)

| Predisposing risk factor(s) | Typical pathogen(s) |
|---|---|
| Prematurity | *S. agalactiae* (group B streptococcus)<br>*Escherichia coli*<br>Other aerobic gram-negative bacilli |
| Very low (VL) and extremely low (EL) birthweight<br>VLBW is less than 1500 grams (3 lbs. 4 oz)<br>ELBW is less than 1000 grams (2 lbs. 3 oz) | *S. agalactiae*<br>*Enterococcus* species<br>Coagulase-negative staphylococci |
| Maternal colonization with *S. agalactiae* (group B streptococcus) | *S. agalactiae* |
| Chorioamnionitis | *S. agalactiae*<br>*Escherichia coli*<br>Other aerobic gram-negative bacilli |
| Prolonged rupture of membranes (greater than 18 hours prior to delivery) | *S. agalactiae*<br>*Escherichia coli*<br>Other aerobic gram-negative bacilli |
| Traumatic delivery | *Escherichia coli*<br>Other aerobic gram-negative bacilli |
| Galactosemia (a rare metabolic disorder) | *Escherichia coli* |
| Congenital anomalies of the urinary tract | *Escherichia coli*<br>Other aerobic gram-negative bacilli |
| Dermal sinus tracts or myelomeningocele | Coagulase-negative staphylococci<br>*Staphylococcus aureus*<br>Aerobic gram-negative bacilli |
| Maternal consumption of unpasteurized dairy products, deli meats, or contaminated produce | *Listeria monocytogenes* |

coccal disease caused by non-vaccine strains became more prevalent. Some of these strains, such as serotype 19A, were particularly problematic because they had developed resistance to several classes of antibiotics, including β-lactams (penicillins and cephalosporins). These observations prompted the development of the next-generation pneumococcal conjugate vaccine with a total of 13 pneumococcal serotypes (PCV13) including serotype 19A. PCV13 was introduced in the USA in 2010, gradually replacing its predecessor. There are approximately 90 serotypes of *Streptococcus pneumoniae* that can infect humans. The 13 serotypes included in PCV13 represent the strains that most commonly caused invasive disease in US children and/or had developed resistance to multiple classes of antibiotics. Any of the remaining 77 or so serotypes that are not included in the current vaccine have the potential to cause invasive disease explaining the observation that disease due to non-vaccine pneumococcal serotypes remains the most common cause of meningitis in children >1 month of age [9, 10].

*N. meningitidis* is the most common cause of bacterial meningitis in adolescents and young adults [11]. The epidemiology of the infection supports two peaks of disease, one among children less than 5 years of age and the other among children and adolescents older than 11 years.

The list of bacterial pathogens that are capable of causing meningitis is extensive, but organisms other than the ones already discussed don't typically do so unless the host is immunocompromised or the pathogen has direct access to the subarachnoid space. Patients who have recently undergone a neurosurgical procedure and those with traumatic or specific congenital anatomic defects are at risk for developing meningitis because the anatomic barriers that typically provide the first line of defense against the entry of bacteria have been disrupted. Table 23.3 highlights several of these predisposing risk factors for the development of meningitis and the typical bacteria associated with each of them.

## 23.3.2 Pathogenesis

*Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae* type b are all known to colonize the human nasopharynx [12]. Nasopharyngeal colonization may be prolonged without the development of disease in the host, but the condition serves as the reservoir for these pathogens which can be easily transmitted from a carrier to a noncarrier. The process that leads to bacterial meningitis typically occurs through the following sequence of events: (1) recent colonization of the nasopharyngeal mucosa, (2) invasion of the bacteria across the mucosa into the bloodstream, (3) hematogenous seeding of and replication within the subarachnoid space, (4) development of an acute inflammatory response within the subarachnoid space, and (5) the presence of clinical symptoms of meningeal inflammation including headache and neck stiffness and pain with flexion – a position that stretches the inflamed meninges [12]. While most cases of meningitis occur secondary to hematogenous seeding of the subarachnoid space during bacteremia, direct invasion of the meninges can also occur. Breaks in the integrity of the usual anatomic barriers to infection from trauma or surgery and congenital anatomic defects may provide such opportunity. Direct extension also occurs on occasion from a contiguous infectious process such as paranasal sinusitis, mastoiditis, orbital cellulitis, or cranial osteomyelitis [13].

Once bacteria enter the subarachnoid space, they replicate quickly because innate immune responses are

**Table 23.3** Predisposing conditions for bacterial meningitis

| Predisposing condition for meningitis | Typical and unusual bacterial etiologies |
|---|---|
| Anatomic or functional asplenia (e.g., congenital, postsurgical, thalassemia, sickle cell anemia) | *Streptococcus pneumoniae*<br>*Haemophilus influenzae* type b<br>*Neisseria meningitidis*<br>*Haemophilus influenzae,* nontypeable<br>*Salmonella* species |
| Anatomic or posttraumatic cerebrospinal fluid leak (e.g., Mondini dysplasia, head trauma with ethmoid, sphenoid or temporal bone fractures) | *S. pneumoniae*<br>*H. influenzae* type b<br>*Haemophilus influenzae,* nontypeable<br>Coagulase-negative staphylococci |
| Cochlear implant | *S. pneumoniae*<br>*H. influenzae* type b |
| Exposure to a close contact with bacterial meningitis | *N. meningitidis*<br>*H. influenzae* type b |
| Penetrating head trauma | *Staphylococcus aureus*<br>Coagulase-negative staphylococci<br>Aerobic gram-negative bacilli |
| Basilar skull fracture | *S. pneumoniae*<br>*Haemophilus influenzae,* nontypeable<br>*Streptococcus pyogenes* (*group A streptococcus*) |
| Recent neurosurgical procedure | Coagulase-negative staphylococci<br>*S. aureus*<br>Aerobic gram-negative bacilli |
| CSF shunt | Coagulase-negative staphylococci<br>*Cutibacterium acnes*<br>*S. aureus*<br>Aerobic gram-negative bacilli |
| Terminal complement deficiency | *N. meningitidis* |
| Humoral immunodeficiency[a] | *Streptococcus pneumoniae*<br>*Haemophilus influenzae* type b<br>*Neisseria meningitidis*<br>*Haemophilus influenzae,* nontypeable |
| Unimmunized, incompletely immunized | *S. pneumoniae*<br>*H. influenzae* type b<br>*N. meningitidis* |

[a]Patients with inherited agammaglobulinemia syndromes such as CD40 ligand deficiency and X-linked Bruton agammaglobulinemia also have a unique predisposition to chronic enteroviral meningoencephalitis

insufficient to inhibit their proliferation [14, 15]. The bacteria and the products of tissue injury associated with the infection initiate a robust inflammatory cascade that results in the recruitment of neutrophils and other leukocytes to the site of infection. Purulent exudate can accumulate rapidly, layering onto cerebral and cerebellar structures, including blood vessels. Depending on the location and thickness of the exudate, a subdural empyema may arise as a complicating feature. If the inflammatory changes in and around the draining veins and venous sinuses are severe, thromboses develop.

Damage to the cerebral cortex occurs via several mechanisms including direct invasion of the bacteria and the subsequent intense host inflammatory reaction, bacterial toxin-mediated effects, venous congestion secondary to thromboses, and impaired blood flow. Cerebral edema leads to elevated intracranial pressure that, when severe, results in brainstem herniation and death. Sufficiently impaired blood flow is associated with cerebral infarctions [12, 14, 16].

## 23.3.3 Clinical Manifestations

There are three basic patterns seen for the clinical presentation of bacterial meningitis: (1) nonspecific symptoms with fever that worsen over a 2- to 5-day period before meningitis is diagnosed; (2) clear signs and symptoms of meningitis, including fever, headache, and stiff neck that develop abruptly over the course of a day or two; and (3) septic shock with rapid clinical decompensation over a few hours [17, 18]. It is important to recognize that neonates and young infants with meningitis present differently than other age groups. Findings that should always raise the possibility of meningitis in this age group include temperature instability, hypothermia, lethargy with poor feeding, and marked irritability. The presence of one or more of these findings should prompt an aggressive approach that includes a diagnostic evaluation for meningitis [18, 19].

### 23.3.3.1 Bacterial Meningitis in Newborns and Young Infants

Newborns and young infants with meningitis may present with subtle signs of infection such as lethargy with poor feeding or marked irritability with an uncharacteristic high-pitched cry [18]. Inconsolable crying in an infant is a nonspecific sign of serious infection or pain. Paradoxical consolability is used to describe an infant that calms when left alone and becomes irritable when held or touched. Infants with meningeal (or peritoneal) inflammation or broken long bone are more comfortable if they are not moved. A finding of paradoxical consolability is nonspecific but should raise suspicion for a condition such as meningitis. Temperature instability with hypothermia is a common finding in newborns with severe infections, including meningitis [20]. Obtaining a thorough history that includes the details of the pregnancy and birth, the presence of any known congenital abnormalities, previous infections, ill contacts, and other exposures helps to guide the differential diagnosis.

On physical examination, a young infant may be irritable due to meningeal irritation. Lethargy and poor tone are common. The anterior fontanelle can be full or bulging, but a normal fontanelle does not rule out meningitis [18]. Additional signs of severe infection may be observed including tachycardia, tachypnea, apnea, or poor capillary refill [19].

#### 23.3.3.2 Bacterial Meningitis Beyond Early Infancy Through Adulthood

Beyond early infancy, the typical manifestations of bacterial meningitis include fever, headache, photophobia, neck stiffness, confusion, irritability, lethargy, nausea, and vomiting. Seizures occur in up to 27% of patients with bacterial meningitis at or before the time of presentation to medical attention [21]. The medical history should be comprehensive including questions about immunization status, predisposing risk factors, any known exposures, recent surgeries, or injuries.

On physical examination, vital signs may show fever, abnormalities in heart and respiratory rates, and/or an unstable blood pressure. Cushing's triad, characterized by bradycardia, hypertension, and respiratory depression, is a late finding of elevated intracranial pressure indicative of impending herniation. The patient may be irritable, lethargic, confused, or combative [22].

Evaluating for the presence of nuchal rigidity is performed using a few simple maneuvers. Pain and stiffness with neck flexion are assessed by asking the patient to touch their chin to their chest. In the uncooperative, or unconscious patient, the maneuver is performed by the examiner. Another technique used to stretch the meninges to determine whether they may be inflamed is called the Kernig sign. Here, with the patient in the supine position, the knee is passively extended while keeping the hip flexed. Resistance to this motion with flexion of the opposite knee is a positive finding. Similarly, if passive neck flexion elicits a reflex flexion of the hips, the patient has a positive Brudzinski sign [23].

A careful and detailed neurologic examination should be performed. Focal neurologic signs including cranial nerve III, VI, and VII palsy are suggestive of increased intracranial pressure. A single fixed, dilated pupil indicates compression of the ipsilateral oculomotor nerve (cranial nerve III) which is concerning for tonsillar herniation. The fundoscopic examination may reveal evidence of papilledema [24]. Unilateral weakness (hemiparesis) suggests ischemia or infarction.

A careful examination of the skin is also important. The presence of a petechial or purpuric rash is most classically associated with *N. meningitidis* infection (meningococcemia) but may also be present in patients with bacterial meningitis caused by other pathogens [25] (Fig. 23.1).

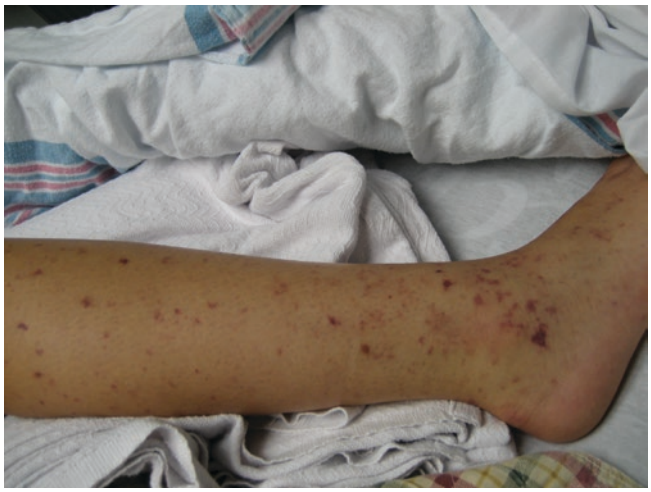

**Fig. 23.1** Petechial rash. Lesions do not blanch with pressure. (Image provided by Dr. Joseph Domachowske)

### 23.3.4 The Diagnostic Evaluation

#### 23.3.4.1 Laboratory Testing: Bloodwork

Blood cultures should be included in the initial testing of all patients with suspected bacterial meningitis. Up to 80% of children and 40% of adults with bacterial meningitis have a positive blood culture [26]. A complete blood cell count with differential may reveal multiple abnormalities, but the findings are nonspecific. Patients with meningitis are at risk for developing disseminated intravascular coagulation (DIC), so thrombocytopenia and abnormal coagulation profiles may be seen [27]. Elevation of blood inflammatory markers, including the C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), are common but not specific findings. Serum electrolytes should be checked and followed during treatment since perturbations may herald the presence of the syndrome of inappropriate antidiuretic hormone (SIADH) secretion, a relatively common complication of bacterial meningitis.

#### 23.3.4.2 Laboratory Testing: Cerebrospinal Fluid

All patients with suspected bacterial meningitis should undergo a lumbar puncture for the collection of cerebrospinal fluid (CSF) unless it is deemed unsafe to do so. During the procedure, an opening pressure can be measured using a manometer. Normal opening pressure varies by age, ranging between 200 and 500 mm $H_2O$ (20–50 cm $H_2O$) in older children and adults. The normal appearance of CSF is clear, like water. It may appear cloudy if the concentration of white blood cells (WBC), red blood cells (RBC), or protein is elevated. Knowledge of the normal ranges for CSF cell counts, glucose, and protein (Table 23.4) is important to help differentiate bacterial meningitis from other diseases. In general, a CSF WBC > 1000 cells/mm$^3$ showing a predominance of neutrophils is suggestive of a bacterial infection, although the range can be quite variable [28]. Bacterial meningitis is also associated with a low, sometimes undetectable, CSF glucose concentration and an elevated CSF protein concentration.

The CSF gram stain may reveal bacteria, and their general morphology (e.g., gram-positive cocci in pairs), but the definitive identification requires that a CSF culture be done. When evaluating a patient for meningitis of an unknown cause, additional testing can be requested that is specific for the identification of acid-fast bacteria, viruses, fungi, and para-

**Table 23.4** Typical biochemical changes seen in cerebrospinal fluid secondary to bacterial meningitis

| Cerebrospinal fluid finding | Healthy newborn | Healthy child or adult | Bacterial meningitis |
|---|---|---|---|
| Total leukocytes (cells/mm$^3$) | <30 | <6 | >1000 |
| Neutrophils (%) | 20–60 | 0 | >85–90 |
| Protein (mg/dL) | 30–150 | 20–40 | >100–150 |
| Glucose (mg/dL) | 30–120 | 40–80 | 0–<40 |
| Positive gram stain (%) | 0 | 0 | >85 |
| Positive culture (%) | 0 | 0 | >95 |

sites. Polymerase chain reaction (PCR)-based diagnostics are becoming more popular. PCR-based panels designed to detect the presence of nucleic acid specific to each of the common bacterial and viral causes of meningitis have been developed. The reported sensitivity and specificity of PCR range between 99% and 100% depending on the organism and the specific test panel [29]. PCR-based testing cannot yet replace bacterial culture since antimicrobial susceptibility testing still requires that the pathogen be recovered in culture.

Lumbar puncture is not always a safe procedure to perform. Contraindications to the collection of cerebrospinal fluid by lumbar puncture include elevated intracranial pressure, hemodynamic instability, severe coagulopathy, or soft tissue infection at the site. In circumstances where it is deemed unsafe to perform the lumbar puncture, empiric antimicrobial therapy should still be initiated immediately.

#### Traumatic Lumbar Puncture

A traumatic lumbar puncture introduces red blood cells into the CSF due to difficulty in obtaining the sample or piercing a blood vessel in the soft tissues prior to entering the subarachnoid space. One formula used to estimate the expected number of WBCs in the CSF from a traumatic LP is to subtract 1 CSF WBC for every 1000 CSF RBC/mm$^3$ [30]. A correction factor result that makes a CSF pleocytosis unlikely should not rule out bacterial meningitis if the clinical suspicion is high. The value of using this or related formulas to "correct" the leukocyte count based on the presence of red blood cells is unclear. Ideally, one should avoid attempts to interpret CSF findings collected by a traumatic lumbar puncture. More reliable information would be derived from repeating the lumbar puncture.

#### 23.3.4.3 Neuroimaging in the Setting of Suspected and Confirmed Bacterial Meningitis

It is not necessary to obtain neuroimaging on all patients with suspected or confirmed bacterial meningitis; however, the relative frequency of infection-related complications does require a high level of vigilance and low threshold for considering it. Computed tomography (CT) scanning of the brain is recommended for all patients who exhibit focal neurologic deficits, have papilledema that is evident on fundoscopic exam, and are comatose. Adult patients with a new-onset seizure disorder, preexisting central nervous system disorder, or underlying serious immunodeficiency should also undergo neuroimaging prior to having a lumbar puncture. CT scan findings in the setting of bacterial meningitis are typically normal otherwise, so there is no need to delay the lumbar puncture and empiric antibiotic therapy waiting for the imaging study to be completed [31, 32].

### 23.3.5 Differential Diagnosis

Patients who present with fever, nuchal rigidity, headache, and vomiting should be suspected of having bacterial meningitis until proven otherwise. Appropriate diagnostic testing and empiric treatment for bacterial meningitis should be continued unless and until meningitis can be excluded. A variety of mycobacteria, viruses, fungi, and parasites also have the potential to cause meningitis. Clues to the presence of one of these alternative etiologies are usually revealed when reviewing the results of the laboratory testing of the cerebrospinal fluid. Other infections and noninfectious disorders that share overlapping clinical syndromes with bacterial meningitis are outlined in Table 23.5.

### 23.3.6 Management

#### 23.3.6.1 Supportive Care

Many patients with bacterial meningitis present with signs and symptoms consistent with sepsis requiring admission to an intensive care unit [33]. Aggressive fluid resuscitation may be required to establish and maintain adequate tissue perfusion. In some cases, inotropic support is also needed. If the patient cannot protect their airway due to seizures or coma, endotracheal intubation and mechanical ventilation are performed.

Frequent neurologic checks should be performed on patients being treated for bacterial meningitis for at least the first 72 h of hospitalization to evaluate for potential emerging complications such as an epidural abscess, subdural empyema, cerebral edema, or cerebral infarction. If elevated intracranial pressure develops, mannitol, hypertonic saline, or hyperventilation can be prescribed while elevating and maintaining the patients' head midline. These interventions and positioning serve to optimize cerebral perfusion and venous drainage [33]. Seizures are a common complication of bacterial meningitis. Anticonvulsant therapy or prophylaxis may be used in the acute setting [14, 24].

Serum electrolytes should be followed closely because patients with meningitis are at risk for developing the syndrome of inappropriate antidiuretic hormone (SIADH) secretion [34]. If there is concern for SIADH, serum and urine osmolality are monitored. Fluid restriction may be necessary.

**Table 23.5** Infectious and noninfectious disorders that share clinical features with bacterial meningitis

| Infections | Noninfectious disorders |
|---|---|
| Other causes of meningitis<br>Mycobacteria, especially tuberculosis<br>Spirochetes (e.g., *Borrelia burgdorferi*)<br>Rickettsia (e.g., *Rickettsia typhi*)<br>Viruses (e.g., enteroviruses)<br>Fungi (e.g., *Cryptococcus neoformans*)<br>Parasites (e.g., *Strongyloides stercoralis*) | Rheumatologic disorders (e.g., systemic lupus erythematosus) |
| Retropharyngeal abscess | Kawasaki disease |
| Brain abscess | Lead poisoning |
| Subdural or epidural abscess | Drug reactions (e.g., intravenous immunoglobulin) |
| Infective endocarditis with septic emboli | Neoplastic meningitis (e.g., melanoma) |
| Cervical spine osteomyelitis | Trauma |
| Cervical spine septic arthritis | Esophageal foreign bodies such as button batteries |

### 23.3.6.2 Antibiotic Treatment of Bacterial Meningitis

Empiric antibiotic treatment decisions for suspected bacterial meningitis are guided by the patient's age, known underlying risk factors, and the suspected pathogens [28]. Empiric antibiotic therapy should start immediately after blood cultures have been obtained and a lumbar puncture has been performed to collect cerebrospinal fluid [35]. Antibiotics should be bactericidal, not bacteriostatic, and their dose should be selected to attain appropriate penetration and concentration in the CSF [36]. If the patient is not improving after 48 h, a repeat lumbar puncture and/or neuroimaging should be considered to evaluate for complications. Bacterial meningitis can be associated with fevers as long as 6 days after initiation of appropriate antibiotic therapy. During this time, the persistence of fever alone is not necessarily concerning if the patient shows other signs of improvement [37]. Consultation with the infectious disease service is appropriate to assist with further diagnostic testing and management.

Antibiotic therapy should be reevaluated when the laboratory has identified the bacterial cause of the infection and reported the final antibiotic susceptibility results [38]. The duration of treatment depends on the clinical picture and etiologic bacteria [28, 38]. If the patient has developed complications such as brain abscess, subdural empyema, delayed sterilization of the CSF, or sinus venous thrombosis, an extended course of treatment is usually planned.

**Table 23.6** Preferred antibiotic therapy for bacterial meningitis with a known microbiologic cause

| Organism | Preferred antibiotic | Treatment duration |
|---|---|---|
| *Neisseria meningitidis* | Third-generation cephalosporin[a] | 7 days |
| *Haemophilus influenzae* type b and nontypeable isolates | Third-generation cephalosporin[a]<br>Ampicillin for β-lactamase negative strains | 7 days |
| *Streptococcus pneumoniae* | Penicillin (if susceptible)<br>Third-generation cephalosporin[a] (if susceptible)<br>Vancomycin (for isolates resistant to the above options) | 10–14 days |
| *Streptococcus agalactiae* | Ampicillin (addition of gentamicin can be considered) | 14–21 days |
| Aerobic gram-negative bacilli | Third-generation cephalosporin[a] (if susceptible)<br>Alternatives based on susceptibility results include cefepime, meropenem, or a fluoroquinolone | 21 days |
| *Listeria monocytogenes* | Ampicillin and gentamicin (the gentamicin can be discontinued after 7 days) | 21 days or longer |

[a]ceftriaxone or cefotaxime

### 23.3.6.3 Treatment of Bacterial Meningitis in Newborns and Young Infants

Newborns with suspected bacterial meningitis can be treated empirically with ampicillin and gentamicin [19]. Some institutions have opted to use ampicillin in combination with a third-generation cephalosporin (cefotaxime) because of local experience with aerobic gram-negative bacilli infections that are resistant to gentamicin. Young infants who have been previously hospitalized and those with congenital anatomic abnormalities should be treated empirically with cefotaxime because of its broader spectrum of coverage. Empiric therapy should be switched to targeted therapy once the bacterial cause of the infection has been identified, and its susceptibility profile is known. The preferred antibiotic(s) and the recommended treatment durations based on the specific pathogen causing the patient's meningeal infection are reviewed in Table 23.6 [28].

### 23.3.6.4 Treatment of Bacterial Meningitis Beyond the Newborn Period

Beyond the newborn period, throughout childhood, adolescence, and young adulthood, empiric antibiotic therapy for meningitis should include a third-generation cephalosporin

such as ceftriaxone or cefotaxime together with vancomycin [28]. The third-generation cephalosporin provides coverage for all isolates of *H. influenzae* and *N. meningitidis* and for the majority of *S. pneumoniae* isolates. Vancomycin is added empirically because some *S. pneumoniae* isolates have developed high-level resistance to all β-lactam class antibiotics [39]. If a penicillin or third-generation cephalosporin-susceptible strain of *S. pneumoniae* is isolated in culture, the vancomycin should be discontinued and the treatment course completed with either penicillin or a third-generation cephalosporin as directed by the bacteria's susceptibility profile. Ampicillin can be used in place of penicillin if necessary. The preferred antibiotic(s) and the recommended treatment durations based on the specific pathogen causing the patient's meningeal infection are reviewed in ◘ Table 23.6.

Empiric antibiotic therapy for adults 50 years and older, and for anyone suspected to have meningitis caused by *Listeria monocytogenes* based on other risk factors or on a CSF gram stain that demonstrates the presence of gram-positive bacilli, should have ampicillin added to their empiric treatment regimen pending culture results. If meningitis caused by *Listeria monocytogenes* is confirmed, targeted therapy includes the combination of ampicillin and gentamicin for 1 week followed by ampicillin alone for a total treatment duration of 21 days or longer (◘ Table 23.6).

#### 23.3.6.5 Adjunctive Therapy in the Treatment of Bacterial Meningitis

Systemic glucocorticoids, usually in the form of dexamethasone, are sometimes used as adjunctive therapy for patients with bacterial meningitis. In children with *Haemophilus influenzae* type b meningitis (now quite rare), adjunctive treatment with dexamethasone reduces the incidence and severity of sensorineural hearing loss if administered prior to or with the first dose of intravenous antibiotics [40]. For children with meningitis caused by either *S. pneumoniae* or *N. meningitidis*, the role for adjunctive therapy with dexamethasone is unclear, and the practice is generally discouraged. In contrast, adults with meningitis caused by *S. pneumoniae* have reduced morbidity and mortality when dexamethasone is used as adjunctive therapy. Complications associated with the administration of systemic dexamethasone include hyperglycemia, gastritis, and rebound fevers upon discontinuation.

### 23.3.7 Prognosis and Long–Term Consequences

Bacterial meningitis is associated with significant morbidity and mortality. Mortality rates vary depending on the specific bacteria and host factors. For example, newborns with *E. coli* meningitis have a mortality rate as high as 20% [41]. Other factors also affect prognosis. [▶ Call Out Box 23.1] Pneumococcal meningitis carries a worse prognosis than either Hib or *N. meningitidis* meningitis [42]. High bacterial burden, a decreased level of consciousness at presentation, and a delay in diagnosis and treatment are all associated with worse outcomes [22, 43].

**Call Out Box 23.1**
**Factors That Affect Prognosis and Outcome of Bacterial Meningitis**
- Age
- Type of infecting bacteria
- Bacterial burden
- Severity of disease when antibiotics are started
- Time to diagnosis and initiation of appropriate antibiotics
- Time needed to achieve sterilization of the CSF

**Call Out Box 23.2**
**Long-Term Complications of Bacterial Meningitis**
- Sensorineural hearing loss
- Cognitive disability
- Developmental delay (children)
- Paresis
- Seizure disorder
- Cortical blindness
- Hydrocephalus
- Hypothalamic dysfunction

In developed countries, approximately 15% of individuals with bacterial meningitis develop long-term neurologic sequelae [44–46]. This rate is higher in developing countries where medical care and availability of optimal treatment regimens are less reliable. Sensorineural hearing loss remains the most frequent complication of bacterial meningitis, occurring in up to 30% of individuals with a history of pneumococcal meningitis [26]. [▶ Call Out Box 23.2] lists additional long-term complications that are seen on a regular basis.

### 23.3.8 Discharge Criteria

Patients with bacterial meningitis are managed in the hospital at least until they are clinically stable, able to maintain adequate enteral nutrition, and are without fever for a minimum of 24–48 h [26]. Because the entire course of antibiotic therapy must be administered via the intravenous route and the length of therapy is dependent on the clinical circumstances and the specific infecting pathogen, the patient must either remain in the hospital for the course of therapy or be an excellent candidate for home infusion therapy. Minimal criteria for home infusion therapy [47] are shown in [▶ Call Out Box 23.3].

### 23.3.9 Follow-up Evaluations

Sensorineural hearing loss affects up to one third of patients with bacterial meningitis; therefore all patients should have their hearing assessed either before or shortly

**Call Out Box 23.3**
**Minimal Criteria for Continued Home Intravenous Antibiotic Therapy**

- Clinically stable for discharge
- Not living at home alone; reliable caretaker(s)
- Immediate access to a working telephone and reliable transportation
- Established tolerance of the expected home antibiotic regimen
- Caretakers have received education and understand the procedures associated with home antibiotic infusions
- Home antibiotic administration times have been specified to optimize adherence
- Regular outpatient follow-up visits to monitor ongoing response to treatment and to identify and treat any antibiotic-related side effects

after hospital discharge [48]. Audiology services should be provided as needed. Patients with severe neurologic sequelae may require inpatient rehabilitation services. Those less severely affected will most certainly benefit from outpatient physical and occupational therapy. Even those who appear well at the completion of antibiotic therapy may be at risk for behavioral difficulties and cognitive challenges [49].

### 23.3.10 Prevention

Vaccines designed to protect against each of the three most common causes of bacterial meningitis, *Haemophilus influenzae* type b, *S. pneumoniae*, and *N. meningitidis*, have proven highly effective at reducing the frequency of their occurrence in every part of the world where they have been successfully introduced. Table 23.7 provides a list of vaccines currently available in the USA, the serotypes of each bacteria that they are designed to protect against, and the current US-based recommended immunization schedules. Globally, some variations exist for the specific types of *S. pneumoniae* and *N. meningitidis* vaccines used. For example, a 10-valent *S. pneumoniae* vaccine is used in South Africa instead of the 13-valent vaccine used in the USA, and a monovalent serotype A conjugate *N. meningitidis* vaccine is used in sub-Saharan Africa where serotype A infection was once so prevalent that the region is referred to as "the meningitis belt."

Patients with suspected bacterial meningitis should be placed under droplet precautions until they have received 24 h of effective antibiotic therapy [50]. In addition, all close contacts of patients with meningococcal meningitis, and some close contacts of patients with *H. influenzae* type b meningitis, should receive post-exposure antibiotic prophylaxis since secondary attack rates for both of these infections remain quite high [51, 52].

**Table 23.7** Immunizations against bacteria that cause meningitis

| Immunization | Recommended schedule for healthy US children and adolescents |
|---|---|
| *Haemophilus influenzae* type b protein conjugate vaccine | Primary series of 2 or 3 doses given at 2 and 4 or 2, 4, and 6 months of age depending on the formulation used<br>Single booster dose between 12 and 15 months of age |
| *Neisseria meningitidis* quadrivalent A, C, Y, and W135 protein conjugate vaccine | First dose given at age 11 or 12 years<br>Booster dose given at age 16 year |
| *Neisseria meningitidis* serogroup B vaccine | Category B recommendation; recommended and administered at the discretion of the provider<br>Two or three dose series depending on the formulation used and circumstances of vaccination (routine vs. outbreak control)<br>Recommended to be given between 16 and 18 years of age |
| *Streptococcus pneumoniae* protein conjugate vaccine, 13-valent including capsular polysaccharides for serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F | Primary series of 3 doses administered at 2, 4, and 6 months of age<br>Booster dose administered between 12 and 15 months of age |

## 23.4 Exercises

Please refer to the supplementary information section for answers to these exercises.

**Case 1 Follow-Up**

A 3-week-old female, born at full-term, is brought to the emergency department because of poor feeding and feeling cool to the touch. Her physical examination shows an irritable infant with a full anterior fontanelle. Her rectal temperature is 36 °C (96.8 °F), heart rate is 180 beats per min, respiratory rate is 60 breaths/min, and blood pressure is 86/52 mm Hg.

1. Which of the following should be considered as possible diagnoses for this neonate?
   A. Bacteremia with sepsis.
   B. Bacterial meningitis.
   C. Bacteremia with sepsis and meningitis.

2. Of the following, appropriate evaluations for this neonate include (select all that apply):
   A. Blood culture.
   B. Cerebrospinal fluid analysis with cell counts, protein, glucose, gram stain, and bacterial culture.

C. Complete blood cell count with differential and platelet count.
D. Urinalysis and urine culture.

3. Figure 23.2 is a photomicrograph of the infant's cerebrospinal fluid gram stain. The *most* likely bacteria responsible for this neonate's meningitis is:
A. *Escherichia coli.*
B. *Listeria monocytogenes.*
C. *Haemophilus influenzae (nontypeable).*
D. *Streptococcus agalactiae.*

4. Of the following, the *most* appropriate treatment for this neonate's bacterial meningitis is:
A. Ampicillin and a third-generation cephalosporin.
B. Ampicillin and gentamicin.
C. Third-generation cephalosporin.
D. Vancomycin.

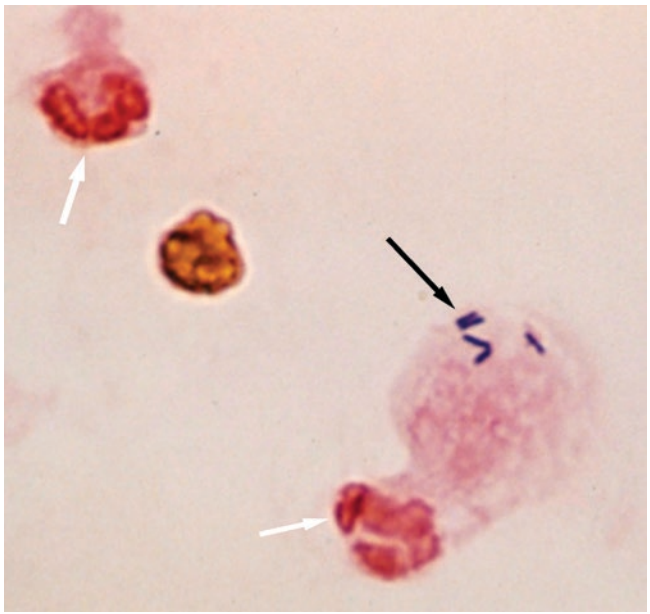

**Fig. 23.2** Gram stain of cerebrospinal fluid obtained from the newborn described in **Exercise Case 1**. Note the presence of neutrophils (*white arrows*). Intracellular rod-shaped bacteria, appearing purple in color, are present inside one of the neutrophils (*black arrow*). (Image provided courtesy of Dr. Joel Mortensen, Ph.D.)

**Case 2 Follow-Up**

A 10-year-old boy presents to the emergency department with a 3-day history of headache, nasal congestion, and fever. Today, he developed swelling and redness around his right eye. He has been otherwise healthy and has received all age-appropriate immunizations.

On physical examination, he is difficult to arouse. His temperature is 38.6 °C, heart rate is 120 beats/min, respiratory rate is 20 breaths/min, and blood pressure is 116/80 mm Hg. He has proptosis (bulging of the eye anteriorly) with marked redness, swelling, and tenderness around his right eye. He is unable to cooperate with an assessment of his extraocular movements. He resists neck flexion.

5. Which of the following should be considered as possible diagnoses for this boy?
A. Bacterial meningitis.
B. Orbital cellulitis.
C. Periorbital cellulitis.
D. Both A and B.

6. Of the following, the *most* appropriate empiric antibiotic therapy for this boy would be:
A. Ampicillin and gentamicin.
B. Ceftriaxone and gentamicin.
C. Ceftriaxone and vancomycin.

**Case 3 Follow-Up**

A 20-year-old man presents to the office with a 4-h history of fever, chills, and vomiting. He "aches all over," including a "bad headache." He is previously healthy and has received all age-appropriate vaccinations, including a seasonal influenza vaccine and two doses of the quadrivalent meningococcal conjugate ACYW135 vaccine at ages 12 and 18 years.

On physical examination, the man appears quite ill. He is drowsy but answers questions appropriately. He asks for the room lights to be turned off stating that the bright lights make his headache worse. His vital signs show a temperature of 39 °C, heart rate of 120 beats/min, and blood pressure of 100/72 mm Hg. His mucus membranes are dry. On auscultation of his heart, his tachycardia has a regular rhythm. A grade II/VI systolic murmur is appreciated along the left lower sternal border. His lung and abdominal examinations are normal. Pinpoint red and dark purple macules that do not blanch with pressure are noted on his feet and lower legs.

7. You arrange for an ambulance to transport the man to the local hospital emergency department. Which of the following is the next *most* appropriate step in this adolescent's management while awaiting transport?
A. Administer intramuscular ceftriaxone.
B. Administer intramuscular dexamethasone.
C. Order computed tomography of the head.
D. Order a rapid test for influenza.

8. Figure 23.3 is a photomicrograph of the patient's cerebrospinal fluid gram stain. Which of the following bacteria is *most* likely responsible for his meningeal infection?
A. *Haemophilus influenzae* type b.
B. *Neisseria meningitidis.*
C. *Streptococcus pneumoniae.*
D. *Listeria monocytogenes.*

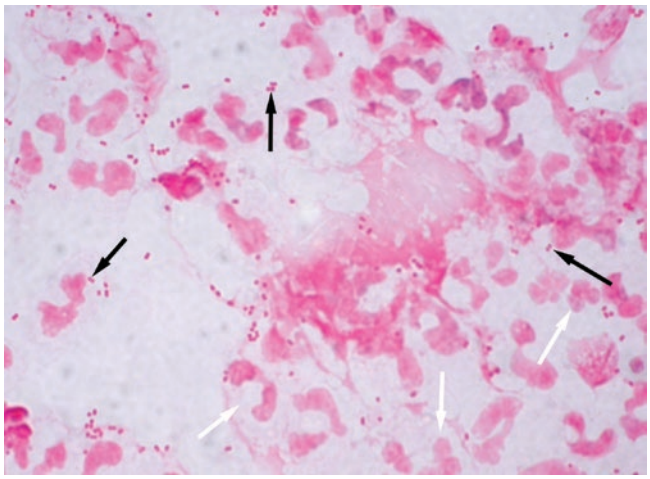

**Fig. 23.3** Gram stain of cerebrospinal fluid obtained from the man described in **Exercise Case 3**. (Image provided courtesy of Dr. Joel Mortensen, Ph.D.)

9. The young man lives at home with his parents and a 14-year-old sister. Of the following, the *most* appropriate immediate intervention for them is:
   A. Vaccination with quadrivalent A, C, Y, and W135 *Neisseria meningitidis* vaccine.
   B. Vaccination with monovalent serogroup B *Neisseria meningitidis* vaccine.
   C. Vaccination with both the quadrivalent A, C, Y, and W135 *Neisseria meningitidis* vaccine and monovalent serogroup B *Neisseria meningitidis* vaccine.
   D. Post-exposure antibiotics.

## 23.5 Summary

Bacterial meningitis is a life-threatening infection that causes leptomeningeal inflammation. A thorough history and physical examination are essential to assess the severity of illness and to identify contributing risk factors. At a minimum, the initial laboratory evaluation should include a cerebrospinal fluid gram stain and culture, cell count, glucose, and protein, blood cultures, a complete blood count, serum electrolytes, and blood cultures. Microorganisms that typically cause meningitis in neonates include *S. agalactiae* and *E. coli*, while *S. pneumoniae* and *N. meningitidis* are the usual culprits in older children, adolescents, and adults. Empiric antibiotic therapy should be selected based on the patient's age and risk factors but typically includes ampicillin and gentamicin for neonates and a third-generation cephalosporin with vancomycin for children and adults. Decisions regarding definitive therapy and total length of treatment depend on the specific pathogen and the clinical course of the disease. Even with appropriate diagnosis and treatment, significant morbidities, such as hearing loss, occur frequently. Age-appropriate immunizations and appropriate antibiotic post-exposure prophylaxis are highly effective interventions toward reducing the total burden of bacterial meningitis.

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# Parameningeal Infections

## Fever, Headache, and An Abnormal Neurologic Examination

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**Learning Objectives**

- Discuss the pathophysiology, predisposing conditions, clinical signs and symptoms, and differential diagnosis of parameningeal infections including brain abscess, spinal epidural abscess, and subdural empyema.
- List the most common etiologic agents of parameningeal infections.
- Identify the most common complications of parameningeal infections.
- Plan the diagnostic evaluation of a patient with a suspected parameningeal infection.
- Describe the management of a patient with a parameningeal infections.

## 24.1 Introduction

Parameningeal infections need to be identified early so that appropriate treatment can be initiated and serious neurologic sequelae prevented. The primary care provider must include these infections in the differential diagnosis of a patient who presents with any combination of symptoms that includes fever, mental status changes, vomiting, headache, back pain, meningismus, or a focal neurological findings. [► Call Out Box 24.1] Many of the signs and symptoms of intracranial infections overlap with those of meningeal infection and should always be included in the differential diagnosis of meningitis. While several predisposing risk factors are known, most patients who develop parameningeal infections are previously healthy. [► Call Out Box 24.2] Once the diagnosis of a parameningeal infection is considered, an appropriate imaging study should be performed. A neurosurgical consultation should be obtained if a parameningeal focus of infection is identified. This chapter includes descriptions of the typical clinical manifestations and management of brain abscess, spinal epidural abscess, and subdural empyema.

## 24.2 Definitions

**Brain abscess** – A focal suppurative infection of the brain parenchyma

**Spinal epidural abscess** – A pyogenic infection of the epidural space along the spine

**Subdural empyema** – A collection of infected material present between the dura and arachnoid

**Call Out Box 24.1**
Parameningeal infections usually present with fever, headache, vomiting, altered mental status, and seizures.

**Call Out Box 24.2**
Predisposing conditions for parameningeal infections include congenital heart disease, sinusitis, odontogenic infections, otitis media, and vertebral osteomyelitis.

## 24.3 Brain Abscess

Brain abscesses are focal intracerebral suppurative infections of the brain parenchyma. The infection begins as a localized area of cerebritis which subsequently evolves through various stages to form an organized, encapsulated collection of pus [1, 2]. The offending organisms most commonly initially gain entry to the brain through either contiguous spread from, hematogenous seeding during bacteremia, or as a complication following penetrating head trauma [1–4]. The most common predisposing conditions for the development of a brain abscess from contiguous spread are chronic sinusitis and suppurative otitis media. The continuous bacteremia or fungemia that is present during infective endocarditis is a well-described risk factor for the development of a brain abscess secondary to hematogenous seeding. With improvement in the treatment and prevention of sinus and middle ear infections, the incidence of brain abscesses linked to contiguous spread from these conditions has decreased in recent years [5].

The development of a brain abscess is distinctively unusual, highlighting the importance of searching for existing predisposing factors that led to its development. Identifying an underlying cause and/or risk factor is likely to influence decisions about optimal empiric antimicrobial therapy, and in some circumstances, such as the presence of infective endocarditis, identify a need for additional subspecialty advice.

The anatomic location of a brain abscess also provides possible clue about the source of the primary infection. Frontal lobe abscesses typically arise from contiguous spread of infection from the frontal or ethmoid sinuses, while temporal lobe and cerebellar abscesses are more likely to arise as complications of otitis media or sphenoid sinus disease. Hematogenous spread of organisms, as occurs in the presence of infective endocarditis, results in brain abscesses along the distribution of the middle meningeal artery.

The clinical manifestations of brain abscess are influenced by multiple factors, including the location and size of the lesion, the virulence of the infecting pathogen(s), and the presence of absence of any associated underlying systemic conditions. Headache is a common and prominent complaint. Other fairly predictable symptoms include fever and vomiting. Early on, changes in mood and behavior may develop. Later changes in mental status may include altered periods of consciousness or coma. Seizures may develop at any time during the infection. The presence of focal neurological signs is largely dependent on the anatomic location of the abscess and its surrounding inflammation. A high index of suspicion for the presence of a brain abscess is required when a patient presents with headache, fever, and vomiting.

All patients suspected to have a brain abscess should undergo emergent neuroimaging to confirm the diagnosis and define the location and extent of the infection. In neonates, cranial ultrasound may be used as the first-line imaging modality since the presence of the open anterior fontanel allows for a direct ultrasonographic evaluation [6, 7]. In older children, adolescents, and adults, conventional

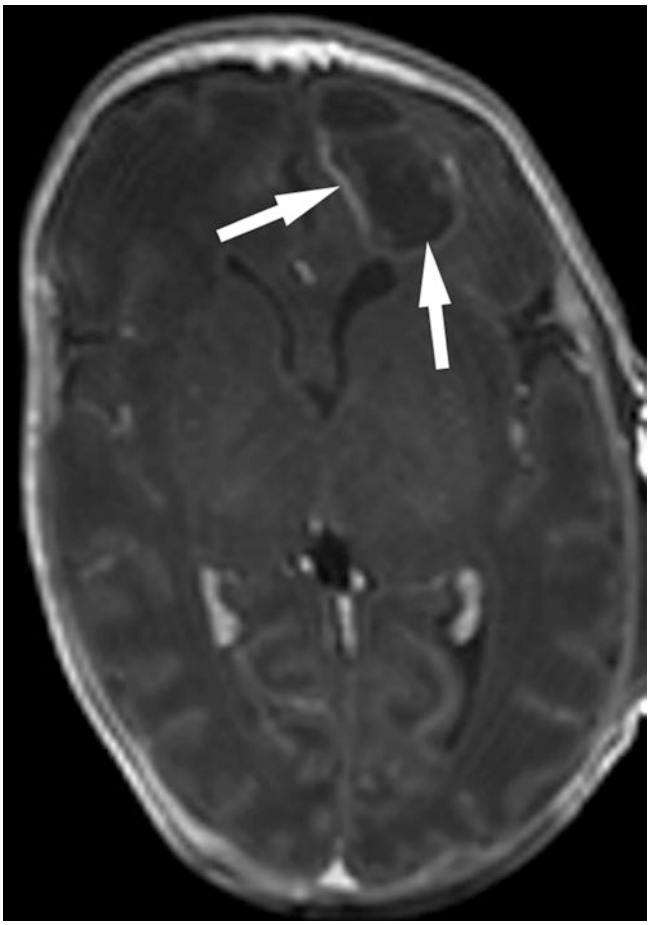


**Fig. 24.1** Axial T1 MRI of this newborn shows a large frontal lobe hypointense lesion with peripheral enhancement consistent with a brain abscess (*arrows*). Cultures performed on material aspirated from the lesion grew *Citrobacter koseri*. (*Courtesy of Dr. Joseph Domachowske*)

**Table 24.1** Typical causes of brain abscess by predisposing condition

| Predisposing condition | Organism(s) |
|---|---|
| Congenital heart disease | Viridans group streptococci[a]<br>*Haemophilus aphrophilus*<br>*Peptostreptococcus* species<br>*Veillonella* species |
| Sinusitis and odontogenic infections | *Staphylococcus aureus*<br>Viridans group streptococci[a]<br>*Peptostreptococcus* species<br>Enteric gram-negative rods<br>*Prevotella* species |
| Otitis media | Viridans group streptococci[a]<br>*Streptococcus pneumoniae*<br>Enteric gram-negative rods<br>*Pseudomonas aeruginosa*<br>*Peptostreptococcus* species |
| Neonate | *Citrobacter koseri*<br>*Streptococcus agalactiae*<br>*Proteus* species<br>*Serratia marcescens*<br>*Enterobacter* species |
| Compromised immune system | *Nocardia* species<br>Fungi<br>A variety of opportunistic bacterial pathogens |

[a]The viridans group streptococci are alpha hemolytic *Streptococcus* species, many of which are normal species of the human gastrointestinal tract. There are six major groups: *S. mutans*, *S. salivarius*, *S. anginosus*, *S. mitis*, *S. sanguinis*, and *S. bovis*

gadolinium-enhanced magnetic resonance imaging (MRI) is the most sensitive and specific technique for the evaluation of a brain abscess [6, 7]. On T1-weighted images, a brain abscess appears hypointense with a strong peripheral enhancement after the administration of gadolinium (Fig. 24.1). On T2-weighted images, a brain abscess has a hyperintense central area surrounded by a well-defined capsule with evidence of adjacent edema. Metastatic brain tumors can share these features on MRI underscoring the importance of consultation with the neuroradiologist prior to performing the scan. The neuroradiologist can then work with the technician performing the scan to optimize the imaging techniques used.

The treatment of a brain abscess requires a multidisciplinary approach. The primary care team should collaborate with the neuroradiologist, the neurosurgeon, and an infectious disease. In some cases, a neurologist and/or cardiologist may also be needed to round out the care team. The initial treatment of a pyogenic brain abscess includes adequate drainage. The surgical procedure may serve to immediately reduce or relieve elevated intracranial pressure. Material collected at the time of surgery allows for confirmation the diagnosis and initiation of a microbiologic analysis. With enhance guided neuroimaging and minimal invasive surgical techniques, stereotactic aspiration has become the surgical method of choice at many centers [1].

Broad-spectrum antibiotics that are known to cross the blood-brain barrier should be initiated immediately after the surgical culture is obtained. De-escalation of the broad-spectrum empiric therapy to more narrow-spectrum antibiotics that specifically and optimally target the organism(s) responsible for the infection should be practiced when culture and susceptibility results are available. The duration of therapy recommended by most experts is between 4 and 6 weeks depending on the extent of the disease and success of the surgical drainage procedure. Longer courses of therapy are used for some pathogens. Table 24.1 lists the microorganisms that are usually responsible for brain abscesses based on the underlying predisposing condition. Table 24.2 lists the usual initial empiric antibiotic therapy used for the treatment of brain abscess when a predisposing condition is known [8]. The most common organisms isolated from brain abscesses that are a result of contiguous spread from a sinus infection or dental abscess are *S. aureus*, viridans group streptococci, enteric gram-negative rods, and *Peptostreptococcus* species. The same bacteria are responsible for brain abscesses that result from

**Table 24.2** Typical causes of brain abscess by predisposing condition: initial empiric treatment

| Predisposing condition | Initial combination of empiric antibiotics[a] |
|---|---|
| Congenital heart disease | Vancomycin, ceftriaxone, and metronidazole |
| Sinusitis and odontogenic infections | Ceftriaxone and metronidazole<br>Consider adding vancomycin to include coverage for methicillin resistant *S. aureus* |
| Otitis media | Ceftriaxone and metronidazole<br>Consider including coverage for *Pseudomonas aeruginosa*[b] |
| Neonate | Ampicillin and cefotaxime |
| Compromised immune system | Vancomycin, ceftriaxone, metronidazole<br>Consider antifungal therapy |

[a]Treatment combinations listed are examples of regimens that include a spectrum of antimicrobial activity expected to include the typical organism(s) involved and have adequate penetration of the blood-brain barrier. Other combinations of broad-spectrum antibiotics with similar spectra of activity and penetration of the blood-brain barrier can also be considered
[b]Antibiotics with a spectrum of activity that usually includes *P. aeruginosa* and have adequate penetration of the blood-brain barrier include ceftazidime, cefepime, meropenem, and ciprofloxacin

contiguous spread from the middle ear along with the notable addition of *Pseudomonas aeruginosa*.

Patients with cyanotic congenital heart disease who present with a brain abscess should initially be treated with antibiotics directed against viridans group streptococci, anaerobic streptococci, and *Haemophilus aphrophilus*. Neonates who develop bacterial meningitis caused by *Citrobacter koseri* have a high incidence of developing brain abscesses as a complication [9, 10].

## 24.4 Spinal Epidural Abscess

A spinal epidural abscess is a suppurative process that involves a localized infection in the epidural space of the vertebral canal. As with most parameningeal infections, epidural abscesses are neurosurgical emergencies which must be identified and treated quickly to minimize the potential for long term-sequelae. The clinical triad of fever, back pain, and a progressive neurologic deficit represent the symptom complex most classically associated with the presence of a spinal epidural abscess, but few patients have all three findings during their initial presentation.

There have been a number of recent reviews on spinal epidural abscesses in adults; [11, 12] however most of the pediatric literature involves either single case reports or small series. A majority of adult patients who develop spinal epidural abscessed have identifiable predisposing conditions such as diabetes mellitus, known intravenous drug abuse, a distant site infection with hematogenous seeding, or a recent invasive procedure [11]. In contrast, most children who develop spinal epidural abscesses are previously healthy with no known predisposing conditions. Children with sickle cell disease and various conditions leading to immunosuppression, however, are more likely than their peers to develop these infections. The presence of back pain in a child with sickle cell disease is most commonly due to the presence of a vaso-occlusive crisis, but may also herald the presence of an epidural abscess [13, 14].

**Table 24.3** Clinical staging of a spinal epidural abscess

| | |
|---|---|
| Stage 1 | Localized back pain |
| Stage 2 | Nerve root pain with radiation |
| Stage 3 | Motor and sensory deficits<br>Bladder and bowel dysfunction |
| Stage 4 | Paralysis |

Most spinal epidural abscesses form either through hematogenous seeding of the organism or by direct extension from a contiguous infection. Hematogenous seeding of the spinal epidural space occurs most commonly from a remote pyogenic infection that is responsible for intermittent periods of bacteremia. Contiguous spread occurs most commonly when vertebral osteomyelitis extends to the spinal epidural space. Children tend to develop more extensive infections than their adult counterparts [14]. Spinal epidural infections damage the spinal cord either by direct physical compression or by causing vascular occlusion secondary to thrombophlebitis, thereby impairing normal blood supply. The clinical stages of a spinal epidural abscess, based on the progression of clinical symptoms, are shown in Table 24.3 [12, 15]. The earliest manifestations of spinal epidural abscess are back pain and fever. As the infection progresses, leg weakness and inability to walk are a frequent complaint [14, 16]. As soon as the diagnosis of spinal epidural abscesses is suspected on clinical grounds, an MRI enhanced with gadolinium should be performed to confirm the diagnosis, identify the location and extent of the infection, and provide anatomic detail so that a decompression procedure can be performed emergently. [▶ Call Out Box 24.3].

**Call Out Box 24.3**
The diagnostic test of choice for parameningeal infection is an MRI with and without contrast.

## Case Study

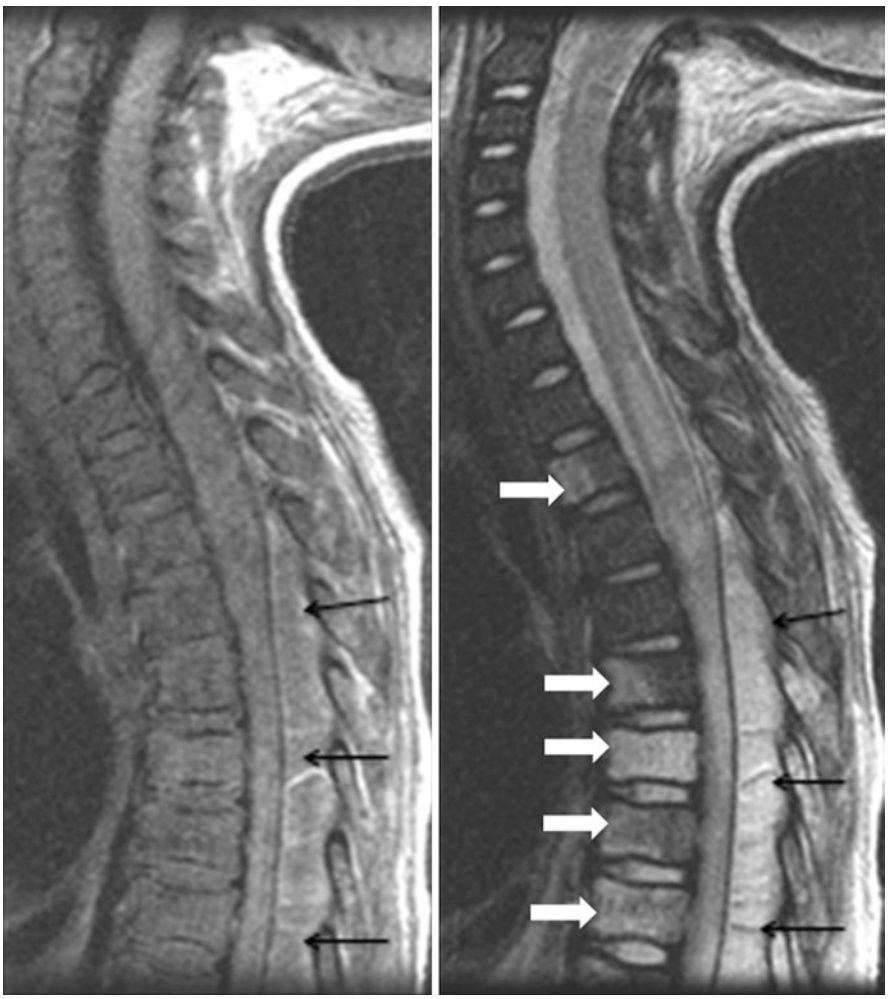
### Practical Examples

A 9-year-old girl with sickle cell disease had been complaining of intermittent back pain for 5 weeks. On physical examination she had a temperature of 39 °C, pain on palpation along her cervical and thoracic spine, and right-hand weakness when attempting to grip tightly. MRI of her spine showed findings consistent with osteomyelitis in several vertebrae and a large spinal epidural collection causing spinal compression (■ Figs. 24.2 and 24.3). An emergent neurosurgical procedure was performed to evacuate the spinal epidural abscess, and treatment with broad- spectrum intravenous antibiotics was started. [▶ Call Out Box 24.4] Blood cultures and cultures of the abscess fluid grew *Salmonella enterica* subsp. enterica.

The laboratory evaluation of patients with spinal epidural abscess typically reveals an elevated total leukocyte count with a predominance of polymorphonuclear leukocytes on the differential. The erythrocyte sedimentation rate (ESR) and C-reactive protein are also usually elevated. These markers of inflammation, although non-specific, may be helpful in monitoring the patient's response to therapy. All patients who are suspected to have a spinal epidural abscess should have blood cultures performed. The results are regularly positive from children, particularly when the pathogenesis of the spinal epidural abscess is via hematogenous spread. The yield of the blood cultures from adults is lower, but should be attempted as one of the ways to secure a microbiologic diagnosis for the infection [17].

Treatment of a spinal epidural abscess should be considered both a surgical and medical emergency. Consultation with a neurosurgeon should occur as soon as the diagnosis is confirmed. Although there is no consensus on the management of a spinal epidural abscess, the typical treatment includes surgical drainage and treatment with intravenous antibiotics. Prompt surgical intervention is recommended to prevent progression of any focal neurological deficits. Neurologic symptoms can progress very quickly [11, 12, 18]. In the absence of focal neurologic findings, some spinal epidural abscesses can be successfully managed non-operatively, with only minimally invasive drainage techniques [16]. Frequent assessment of the patient to identify the presence of any new or worsening neurologic findings is important.

*S. aureus* is the most common cause of spinal epidural abscesses [14, 16]. Antimicrobial treatment should be directed toward coverage of *S. aureus*, including methicillin resistant Staphylococcus aureus (MRSA). Vancomycin should, therefore, be included in the empiric treatment of spinal epidural abscess pending definitive culture and antibiotic susceptibility results. In addition to treatment with vancomycin, a third- or fourth-generation cephalosporin, such as ceftriaxone or cefepime, may be added to the initial antimicrobial regime to cover the possibility of infection caused by gram-negative bacilli. This is particularly important for patients with sickle cell disease, because *Salmonella* species are second only to *S. aureus* as a cause of vertebral osteomyelitis with or without contiguous spread to the spinal epidural space [13, 14].



■ **Fig. 24.2** Sagittal T1 (*left panel*) and T2 (*right panel*) MRIs of the cervical and thoracic spine demonstrating multiple areas of abnormal bone marrow signal most consistent with vertebral osteomyelitis (*white arrows*). A large posterior epidural abscess (*black arrows*) with severe spinal cord compression is noted. (*Courtesy of Dr. Alan Johnson*)

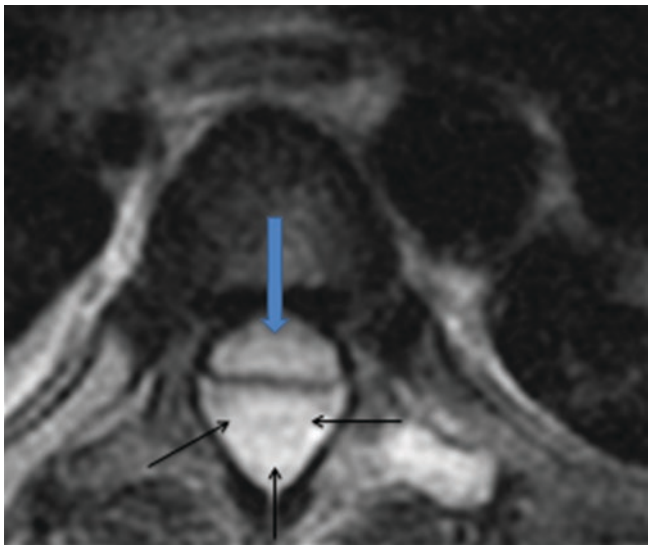


**Fig. 24.3** Axial T2 MRI demonstrates a large dorsal epidural abscess (*black arrows*) with cord compression. Increased T2 signal in spinal cord consistent with edema or infarction (*blue arrow*). (*Courtesy of Dr. Alan Johnson*)

**Call Out Box 24.4**
Parameningeal infections are medical and surgical emergencies.

## 24.5 Subdural Empyema

Subdural empyema is defined as a suppurative collection in the potential space between the dura mater and arachnoid mater. An intracranial subdural empyema can develop as a consequence of bacterial meningitis or as a complication of chronic sinusitis or otitis media [19]. Spinal subdural empyemas are extremely uncommon [20].

Subdural empyema, as a complication of bacterial meningitis, is most common among children less than 1 year of age [9, 19]. The development of this complication should be considered when an infant with meningitis has persistent fevers despite treatment with appropriate antibiotics or develops a worsening neurologic status [9, 19, 21–24]. In contrast, the majority of subdual empyemas that occur in older children, adolescents, and adults develop as a consequence of direct extension from chronic paranasal sinus or the middle infection [21]. The frontal sinuses are most commonly implicated; however the maxillary and ethmoid sinuses also play a prominent role. It is not unusual to observe pansinusitis on imaging studies that demonstrate the presence of a subdural empyema [21, 24, 25], Paranasal sinus infection can spread to the subdural space in one of two ways. First, infection can spread to the subdural space directly from the sinuses by eroding the bony sinus wall, particularly along the lamina papyracea, the thin, smooth, bony structure that forms the lateral wall of the ethmoid and a large portion of the medial wall of the orbit. Second, infection-associated thrombophlebitis can extend in retrograde fashion via the diploic bridging veins of the cranium [▶ Call Out Box 24.5] [25]. The clinical signs and symptoms associated with subdural empyema include fever, headache, vomiting, altered level of consciousness, focal neurological symptoms, seizures, orbital edema, and forehead swelling [▶ Call Out Box 24.6] [24–26].

Most cases of otitis media run an uncomplicated course, either resolving spontaneously or in response to a brief course of outpatient antibiotic treatment. Rarely, middle ear infections lead to serious complications with substantial morbidity. Contiguous extension of a middle ear infection can lead to mastoiditis, sinus venous thrombosis, meningitis, and intracranial infection. Up to 20% of subdural empyemas occur as complications of middle ear infections [9, 27, 28]. Patients with subdural empyemas complicating middle ear infections may have mastoid swelling and otorrhea along with the other typical symptoms of fever, headache, and vomiting.

MRI is the imaging modality of choice for the detection of subdural empyema because it is superior to computer tomography (CT) scan for the detection of small collections [6]. With conventional MRI, subdural empyemas are typically T-1 isodense and T-2 hyperdense with prominent dural enhancement after intravenous gadolinium contrast administration [7].

**Call Out Box 24.5**
The large, thin-walled valveless blood vessels that channel along the spongy, porous bony tissue present between the hard inner and outer walls of the skull are called **diploic** veins. Diploic veins can carry infecting pathogens directly from an infected sinus cavity into the subdural space.

**Call Out Box 24.6**
Forehead swelling associated with frontal sinusitis, subperiosteal abscess formation, and frontal bone osteomyelitis is referred to as **Pott's puffy tumor**. The infection can spread posteriorly leading to cortical vein thrombosis, subdural empyema, and brain abscess. Pott's puffy tumor should not be confused with Pott's disease, which refers specifically to chronic tuberculous vertebral osteomyelitis although both entities were first described by the same British surgeon, Sir Percivall Pott, during the late 1700s.

## Case Study

### Practical Examples

A 21-year-old man complained of worsening headaches for 8 days. Taking over-the-counter pain relievers no longer alleviates the pain. He has had fevers and chills for the last several days. Two days ago, he developed intermittent episodes of vomiting. Additional medical history reveals that he was diagnosed with a viral upper respiratory tract infection 3 weeks ago and states that he has had nasal congestion since that time. On physical examination, the man appears ill. His temperature is 38.8 °C. He has moderate diffuse tenderness overlying his frontal and maxillary sinuses. His neurologic examination is normal exceed for severe photophobia, preventing an adequate fundoscopic examination. The remainder of his physical examination is unremarkable. A clinical diagnosis of acute bacterial sinusitis is made, but the persistence and severity of the headaches with associated episodes of vomiting suggest the possibility of an intracranial complication such as a subdural empyema or brain abscess. A gadolinium-enhanced MRI is performed, confirming the presence of frontal sinusitis and revealing an associated subdural empyema (Figs. 24.4 and 24.5).

The microbiology of subdural empyemas is reflected in the origin of the infection. The organisms most typically associated with infections that originate from the paranasal sinuses include anaerobic and aerobic streptococci, particularly members of the *S. anginosus* group; Haemophilus species; and other anaerobes that typically inhabit the human nasopharynx, such as *Prevotella* species and, less commonly, *S. aureus*. Rarely, gram-negative aerobic bacilli are identified in cultures of the evacuated pus. In addition to the bacterial pathogens listed above, *P. aeruginosa* should also be considered as a possible cause of any subdural empyema that results from the contiguous spread of middle ear space infections [3, 19, 21, 24–26].

The optimal treatment of subdural empyema requires the involvement of a multidisciplinary team that includes a hospitalist or intensivist, a neurosurgeon, a neuroradiologist, an infectious disease specialist, and, in some cases, an otolaryngologist and/or neurologist. Broad-spectrum antibiotic therapy should be started immediately since subdural empyema is a life-threatening, typically polymicrobial infection that can be caused by an extensive list of potential pathogens. One typical antibiotic regimen that includes activity against all of the usual suspects is vancomycin, a third- or fourth-generation cephalosporin and metronidazole [ 3, 19, 21, 24–26]. The optimal duration of antibiotic treatment has not been studied systematically; however 4–6 weeks is usually adequate. The patients should be monitored closely, as longer treatment courses may be necessary in some cases.

An emergency neurosurgical evaluation should always be obtained as soon as the diagnosis of subdural empyema is confirmed since surgical drainage is often necessary. Small, low-viscosity collections may be amenable to burr-hole drainage, while larger, more extensive collections may require a craniotomy for improved outcome [3, 23, 28]. If the paranasal sinuses are the underlying source of the central nervous system infection, simultaneous consultation with an otolaryngologist is prudent since surgical drainage and debridement of the involved areas appear to improve outcome [29].

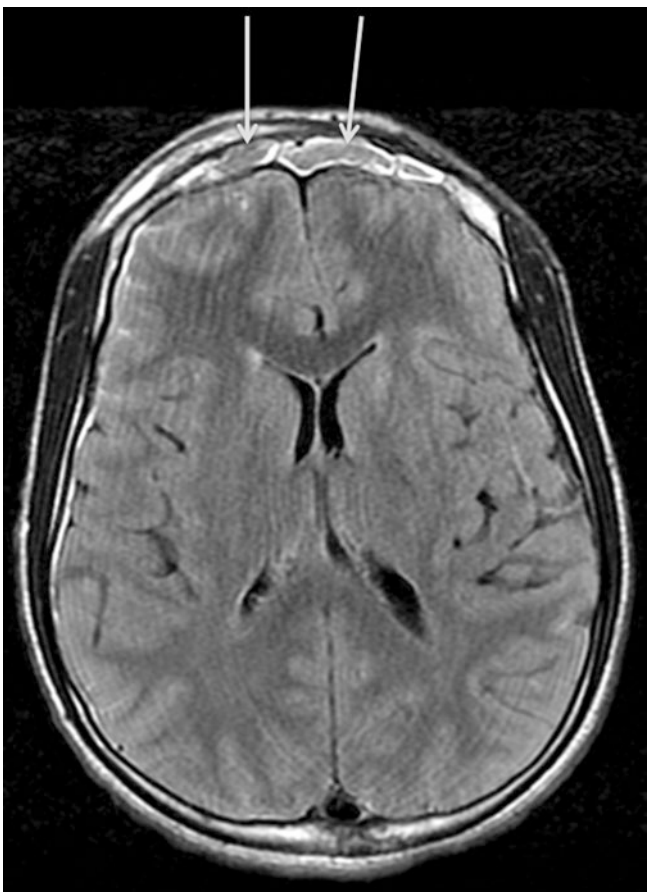


**Fig. 24.4** Axial FLAIR MRI demonstrates extensive opacification of the frontal sinus (*arrows*) consistent with sinusitis. (*Courtesy of Dr. Alan Johnson*)

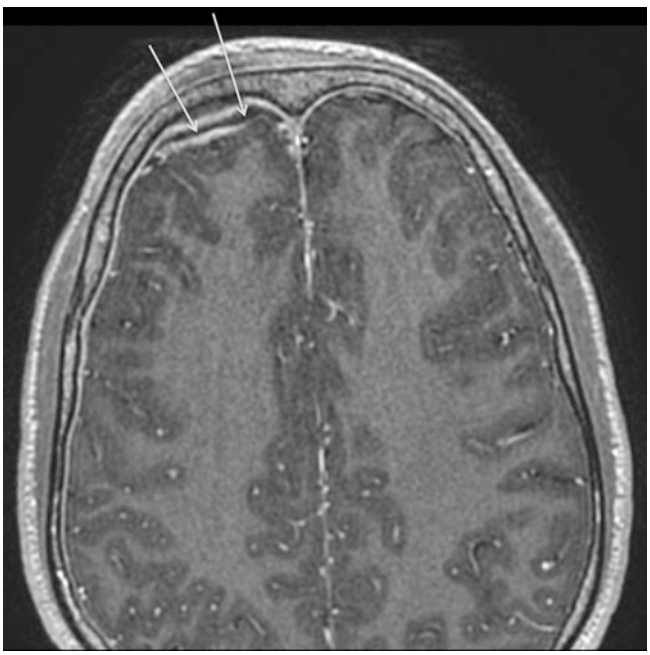


**Fig. 24.5** Axial T1 diffusion-weighted MRI after injection of contrast demonstrates a peripherally enhancing right frontal subdural collection with increased diffusion signal consistent with subdural empyema (*arrows*). (*Courtesy of Dr. Alan Johnson*)

## 24.6 Exercises

Please refer to the supplementary information section for answers to these exercises.

1. What is the most common complaint in a patient with a brain abscess?
2. What is the primary predisposing risk factor for the development of a brain abscess caused by either *Streptococcus agalactiae* or *Citrobacter koseri?*
3. Spinal epidural abscesses typically arise from the direct extension of a primary infection located where?
4. What is the most common microbiologic cause of epidural abscess?
5. Subdural empyema is a known complication of bacterial sinusitis. Which sinuses are most commonly implicated?

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# Meningoencephalitis

## Fever, Altered Level of Consciousness, Seizures

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**Learning Objectives**

- Describe the infectious etiologies of meningoencephalitis.
- Recognize distinguishing clinical features of meningoencephalitis by etiology.
- Identify possible etiologies for meningoencephalitis by identified risk factors.
- List the appropriate diagnostic tests that should be considered during the evaluation of a patient with meningoencephalitis.

## 25.1 Definitions

***Meningoencephalitis*** - inflammation of the meninges and the brain parenchyma

***Rhomboencephalitis*** - inflammation of the brainstem

***Hypoglycorrhachia*** - an abnormally low glucose concentration detected in the cerebrospinal fluid

Meningoencephalitis, defined as inflammation of the brain parenchyma and the surrounding meninges, manifests as cerebral dysfunction often resulting in permanent neurologic sequelae. The underlying cause of the problem frequently goes undetected, even after thorough diagnostic evaluation. Precise etiologies, when identified, include infection, autoimmune disease, vasculitis, neoplasm, and metabolic disorders [1, 2]. The focus of this chapter is on infectious causes of meningoencephalitis [▶ Call Out Box 25.1].

## 25.2 Clinical Evaluation

Meningoencephalitis is an acute disease process that presents with fever and headache together with signs of both meningeal irritation, such as nuchal rigidity and cerebral inflammation manifesting as an altered mental status, abnormal behavior or speech, focal neurologic deficits, and/or new-onset seizures [3, 4] [▶ Call Out Box 25.2]. The evaluation of a patient with suspected meningoencephalitis should begin with a thorough history and physical examination. The age, past medical history, and medication list may identify patients at risk for intracranial hemorrhage, cerebral vasculitis, or central nervous system (CNS) depression, all potential mimics of meningoencephalitis that is caused by infection. Medications that by themselves, can cause symptoms consistent with meningoencephalitis, include amoxicillin, methylphenidate, rituximab, ibuprofen, and immunoglobulin intravenous (IgIV) [5–8]. A vaccination history could highlight increased risk for meningoencephalitis due to vaccine-preventable diseases, including varicella, measles, mumps, and polio. A prolonged duration of symptoms, particularly with no history of fever or systemic illness, is more suggestive of an intracranial mass, while the history of a respiratory tract infection or nonspecific febrile illness days to weeks before the development of neurologic symptoms suggests a post-infectious process, such as acute disseminated encephalomyelitis (ADEM) [9].

**Call Out Box 25.1**
All patients with suspected infectious meningoencephalitis should be treated empirically with intravenous acyclovir until herpes simplex virus infection has been ruled out.

**Call Out Box 25.2**
Clinically, meningoencephalitis includes features of both meningitis and encephalitis.

| Meningoencephalitis | | |
|---|---|---|
| **Meningitis** | **Encephalitis** | **Typical of all CNS infections** |
| Nuchal rigidity | Altered mental status | Fevers |
| Positive Kernig sign | | Headache |
| Positive Brudzinski sign | Focal neurologic deficits | Photophobia |
| | Seizures | |

Epidemiologic data and details learned by taking a thorough travel history may offer clues regarding the etiology since several of the known infectious causes are restricted to specific geographic locations or are more likely to circulate during certain times of the year (Table 25.1). For example, Powassan virus causes disease in Northeastern and Northcentral United States and the bordering areas of Canada, disease caused by Colorado tick fever is restricted to the Western United States, and cases of tick-borne encephalitis virus are seen predominately from Europe and Asia [10–13]. Furthermore, enteroviral disease peaks during summer, while arboviruses are transmitted in areas where their mosquitoes and ticks vectors thrive. Herpes simplex virus infections occur year-round [1]. A thorough exposure history may also provide clues to the etiology of disease process. For example, a history of swimming in warm freshwater lakes should raise the suspicion for the diagnosis of infection by *Naegleria fowleri*, while a history of cat scratches suggests *Bartonella henselae* infection as the trigger (Table 25.1).

Patients clinically suspected to have meningoencephalitis should undergo a complete physical examination with extra care to focus on overt or subtle neurologic findings. The clinical presentation and degree of symptom severity are determined by the anatomic component of the central nervous system that is affected. Encephalitis, or inflammation of the cerebral parenchyma, presents with a disturbance in brain function, with signs and symptoms that include altered mental status, changes in behavior or speech, and seizures. Very few pathogens are described as causing isolated

**Table 25.1** Infectious etiologies of meningoencephalitis to consider based on known exposures

| Exposure | Infectious etiologies to consider |
|---|---|
| Warm freshwater | *Naegleria fowleri* or other free-living amoebae |
| Arthropod bites | |
| Mosquitoes | WNV, EEE, WEE, VEE, SLE, JEV, La Crosse virus, Zika virus, *Plasmodium* spp. |
| Ticks | *Borrelia burgdorferi*, Powassan virus, rickettsia, Colorado tick fever virus, TBE |
| Animal contact | |
| Cats | *Bartonella henselae*, *Coxiella burnetii*, *Toxoplasma gondii* |
| Dogs, skunks foxes | Rabies virus |
| Bats | Rabies virus, Nipah virus |
| Macaque monkeys | Herpes B virus |
| Rodent excretion | Lymphocytic choriomeningitis virus |
| Raccoons | *Baylisascaris procyonis*, rabies virus |
| Geography | |
| United States—East | *B. burgdorferi*, Powassan, EEE, WNV, La Crosse virus, SLE, rickettsia, *Histoplasma capsulatum* |
| United States—West | WEE, WNV, Colorado tick fever, SLE, rickettsia, *B. burgdorferi*, *Coccidioides immitis* |
| Central/South America | EEE, Rabies, SLE, VEE, WEE, WNV, *Plasmodium* spp., rickettsia |
| Europe | TBE, WNV, *B. burgdorferi* |
| Australia | Hendra virus, JEV, *H. capsulatum* |
| Asia | Nipah virus, JEV, *Plasmodium* spp., rabies, WNV, *B. burgdorferi*, TBE, Powassan, *H. capsulatum* |
| Africa | Rabies virus, WNV, *Plasmodium* spp., *H. capsulatum* |

*WNV* West Nile virus, *EEE* eastern equine encephalitis virus, *WEE* western equine encephalitis virus, *SLE* St. Louis encephalitis virus, *JEV* Japanese encephalitis virus, *VEE* Venezuelan equine encephalitis virus, *TBE* tick-borne encephalitis virus

**Table 25.2** Signs and symptoms associated with meningoencephalitis that may offer clues about the underlying etiology

| Associated signs/symptoms | Suggested underlying etiologies |
|---|---|
| Vesicular rash | VZV, HSV, EV, herpes B virus |
| Maculopapular rash | HHV-6, WNV |
| Parotitis | Mumps |
| Gastrointestinal prodrome | Shigellosis |
| Respiratory prodrome | *Mycoplasma pneumoniae*, influenza viruses |
| Lymphadenopathy | CMV, EBV, WNV, HIV, measles, *Bartonella henselae* |
| Urinary symptoms | SLE |
| Pneumonia | Adenoviruses, Nipah virus, Hendra virus, VEE, *Coxiella burnetii*, *Histoplasma capsulatum* |
| Flaccid paralysis | WNV, EV, JEV, TBE, poliomyelitis virus |
| Isolated tremors | SLE |
| Cerebella ataxia | EBV, VZV |
| Cranial nerve deficit | EBV, HSV, VZV, *Borrelia burgdorferi*, *Mycobacterium tuberculosis*, *Coccidioides immitis* |
| Rhomboencephalitis | EV-71, HSV, WNV |
| Hydrophobia, aerophobia, pharyngeal spasm | Rabies |

*VZV* varicella zoster virus, *HSV* herpes simplex virus, *EV* enterovirus, *HHV*-6 human herpesvirus-6, *WNV* West Nile virus, *CMV* cytomegalovirus, *EBV* Epstein-Barr virus, *HIV* human immunodeficiency virus, *SLE* St. Louis encephalitis virus, *VEE* Venezuelan equine encephalitis virus, *HSV* herpes simplex virus

encephalitis, that is, without associated meningeal inflammation. Two viruses that are known to be associated with encephalitis without necessarily causing an associated meningitis are rabies and herpes simplex virus.

Specific focal neurologic findings may provide hints as to the etiology of the central nervous system disease. For example, the findings of cranial nerve deficits, in addition to meningoencephalitis, can be seen in patients infected with *Borrelia burgdorferi*, *Mycobacterium tuberculosis*, and varicella zoster virus [14–16]. Flaccid paralysis is a classic presentation of neuroinvasive West Nile virus infection [17]. Meningoencephalitis that primarily involves the temporal lobe strongly suggests herpes simplex virus as the underlying etiology, although herpes simplex can involve any or all parts the brain. Cerebellar dysfunction can be seen in patients infected with varicella zoster virus or *Mycoplasma pneumoniae* [15, 18]. Rhomboencephalitis is most typical for infections caused by enterovirus 71, West Nile virus, and herpes simplex virus [19]. The presence of new-onset seizures can occur with meningoencephalitis from any cause, while isolated tremors are more characteristic of St. Louis encephalitis virus infection [20–23].

While the focus of the physical examination is the neurologic component, a thorough evaluation of the other organ systems should also be performed in search of additional clues (Table 25.2). The presence of a vesicular rash is typical

during infection with varicella zoster virus and some enteroviruses. The presence of parotitis suggests mumps infection, particularly in unvaccinated individuals. The finding of generalized lymphadenopathy in a patient with meningoencephalitis suggests several possible infectious causes including Epstein-Barr virus, West Nile virus, and human immunodeficiency virus. Measles virus infection can also cause meningoencephalitis in association with generalized lymphadenopathy, but in this case, the other classic findings of measles, cough, coryza, conjunctivitis, and a morbilliform rash will also be present. A respiratory prodrome followed by acute meningoencephalitis is consistent with infection by influenza virus or *M. pneumoniae*, while acute onset of meningoencephalitis following a gastrointestinal prodrome has been described with rotavirus infection [1, 18, 24]. Fever and seizures that can mimic meningoencephalitis are also seen regularly in patients with intestinal shigellosis, but the central nervous system manifestation is secondary to the effects of a bacterial toxin, not from central nervous system invasion by the organism itself. Neonates with meningoencephalitis caused by herpes simplex virus, enteroviruses, adenoviruses, or human parechoviruses can present with viral sepsis with associated hepatitis, pneumonia, and/or rash [25–27].

## 25.3 Diagnostic Evaluation

Cerebrospinal fluid (CSF) analysis is essential in the diagnostic evaluation of patients with suspected meningoencephalitis [28–30]. It is important to note, however, that a lumbar puncture should not be performed on patients with intracranial masses or midline shift, hemodynamic instability, respiratory failure, signs of disseminated intravascular coagulopathy, taking anticoagulation medications, or who are known to have severe thrombocytopenia [29]. Indications for obtaining neuroimaging prior to performing lumbar puncture include impaired consciousness, signs of increased intracranial pressure (such as papilledema or bradycardia with hypertension), focal neurologic deficits, new-onset seizures, immunocompromised state, or a prior history of a central nervous system leison [29].

If there are no contraindications to performing the lumbar puncture, the procedure should be performed without delay. Opening pressure should be documented, and generous amounts of CSF collected to be sure there is sufficient fluid available to allow the laboratory technicians to perform all of the desired diagnostic tests. Routine CSF analysis should include a total nucleated cell count with differential, the concentrations of glucose and protein, a Gram stain, and a bacterial culture. CSF findings typically seen in cases of viral meningoencephalitis include a CSF pleocytosis with a mononuclear cell predominance, an elevated protein concentration, and a normal or slightly depressed glucose concentration [31–35]. Less commonly, the CSF may be acellular or show a pleocytosis with a neutrophilic predominance, especially when sample is obtained very early in the course of infection. Since most patients with meningoencephalitis have normal or only slightly depressed CSF glucose concentrations, results showing the characteristic findings of CSF pleocytosis with a mononuclear cell predominance and elevated protein concentration in association with a moderate to profound hypoglycorrhachia should immediately be recognized as highly unusual and inconsistent with a viral etiology. The CSF analysis pattern described is absolutely classic for *Mycobacterium tuberculosis* infection and, less commonly, fungal meningitis [1, 31, 32]. Immediate recognition that the CSF findings are unusual and classically seen with central nervous system tuberculosis infection, and less commonly in patients with fungal disease, is essential for two reasons. First, medications are available for the treatment of both *M. tuberculosis* and fungal central nervous system infections, so an appropriate empiric antimicrobial treatment regimen can be started without further delay. Second, testing for these pathogens is not a routine or automatic procedure in microbiology, so the clinical microbiology team should be contacted to be sure that all appropriate cultures and other diagnostic studies have been included in their laboratory work-up. Of note, patients with noninfectious causes of meningoencephalitis typically have fewer cells observed in their CSF compared to those with infectious etiologies [32, 34, 35]. The presence of red blood cells in the CSF is often simply blamed on trauma to a small blood vessel in the path of the spinal needle during the lumbar puncture, but it is important to remember that their presence could also indicate the presence of blood in the subarachnoid space secondary to hemorrhagic meningoencephalitis. Infections with a hemorrhagic component due to herpes simplex virus, herpes B virus, and parasitic infections, like *Angiostrongylus cantonensis*, and primary amebic meningoencephalitis is quite typical [36–38].

A CSF analysis profile that includes pleocytosis, with the presence of eosinophils, should also be recognized as highly unusual. The observation is a clue that the patient's meningoencephalitis could be caused by a roundworm, such as such as *Baylisascaris procyonis*, and should likewise trigger a call to the microbiology team to be sure all appropriate diagnostic studies are underway. *B. procyonis* infection is seen almost exclusively in young children with pica and those who have had contact with infected raccoon feces [39].

Further diagnostic testing to determine a specific infectious etiology for meningoencephalitis is driven by the epidemiologic circumstances, known and potential exposures, and other clues discovered during the history and physical examination. Identification of the infecting organism may involve direct visualization on CSF wet mount or after staining, culture, polymerase chain reaction (PCR), serologic testing, or other methods (Table 25.3). Historically, the isolation of viruses from spinal fluid culture was the primary diagnostic method for patients with a viral CNS infection. However, the availability of PCR testing has dramatically improved diagnostic yield over traditional viral cultures. The sensitivity of CSF cultures is very low and when successful often requires days to weeks. On the other hand, PCR testing

**Table 25.3** Diagnostic tests for infectious agents causing meningoencephalitis

| Pathogen | Appropriate diagnostic studies |
|---|---|
| Viruses | |
| Herpesviruses | |
| Herpes simplex viruses 1 and 2 | CSF PCR, surface viral cultures or PCR (neonates), DFA or PCR of skin, mouth, and/or genital lesions |
| Varicella zoster virus (VZV) | CSF PCR, CSF VZV IgM, IgM and IgG serologies, DFA of skin lesion |
| Epstein-Barr virus | CSF PCR, IgM, and IgG serologies |
| Cytomegalovirus | CSF PCR, IgM, and IgG serologies |
| Human herpes virus 6 | CSF PCR |
| Enteroviruses | CSF PCR, PCR on respiratory sample, stool culture |
| Respiratory viruses | |
| Influenza virus | Antigen testing or PCR of respiratory sample |
| Measles virus | CSF PCR, CSF measles IgM, IgM and IgG serologies, culture or PCR of nasopharyngeal or urine sample |
| Mumps virus | CSF PCR, IgM and IgG serologies, culture of saliva or urine |
| Adenovirus | PCR of respiratory sample |
| Arboviruses[a] | CSF PCR (if available), CSF virus-specific IgM, IgM, and IgG serologies |
| Human immunodeficiency virus | IgG serology, quantitative RNA PCR, CSF PCR |
| Rabies virus | Immunofluorescent antigen test performed on skin snip taken from the nape of the neck or on corneal impressions (earliest, and most sensitive diagnostic test), salivary PCR, viral culture of saliva, CSF PCR, CSF virus-specific IgM, IgM, and IgG serologies |
| Bacteria | |
| *Borrelia burgdorferi* | IgM and IgG serologies using two-tier testing (EIA with Western blot confirmation) |
| *Bartonella henselae* | IgM and IgG serologies |
| *Coxiella burnetii* | IgM and IgG serologies |
| *Mycoplasma pneumoniae* | PCR of respiratory sample, IgM and IgG serologies |
| Rickettsial infections | IgM and IgG serologies |
| *Mycobacterium tuberculosis* | Purified protein derivative skin testing, Interferon gamma release assay using whole blood, large volume CSF culture (10 ml or more) |
| Fungal | |
| *Cryptococcus neoformans* | CSF antigen testing, CSF fungal culture, CSF multiplex PCR |
| *Histoplasma capsulatum* | IgM and IgG serologies for yeast and mycelial phases, urine antigen, CSF fungal culture |
| *Coccidioides* species | IgM and IgG serologies, CSF fungal culture |
| Amoeba | |
| *Naegleria fowleri* | Direct visualization in CSF on wet mount or stain. Culture using a lawn of *E. coli* bacteria, PCR of CSF or brain biopsy sample |
| *Acanthamoeba* species | PCR of CSF or brain biopsy sample |
| *Balamuthia mandrillaris* | PCR of CSF or brain biopsy sample |

[a]Including but not limited to West Nile virus, Japanese encephalitis virus, Powassan virus, Western equine virus, Eastern equine virus, La Crosse virus, and St. Louis encephalitis virus

is now available for the more common viral etiologies of meningoencephalitis as a timely highly sensitive diagnostic assay [4, 40]. It is important to understand that while PCR testing has high sensitivity and specificity for many viruses, this does not hold true for all causative agents of meningoencephalitis [4, 41]. Viruses for which PCR testing has proven useful include herpes simplex virus, enteroviruses, Epstein-Barr virus, cytomegalovirus, varicella zoster virus, human herpes virus-6, adenoviruses, human immunodeficiency virus, JC virus, rabies virus, and some of the arboviruses, including eastern equine encephalitis virus, St. Louis encephalitis virus, and the California serogroup viruses [28–30, 40, 42]. It is important to note, however, that detection of viral genome fragments in the spinal fluid, using PCR, should be interpreted carefully as the presence of specific nucleic acid may not actually correlate with the acute disease process. The detection of virus-specific IgM antibody in CSF is also quite useful for identifying the etiologic agent of meningoencephalitis, but generally later in the course of disease, when PCR assays may be negative. The detection of virus-specific IgM in CSF is particularly useful for the diagnosis of VZV and arboviruses infections. For example, the earliest and most sensitive assay used for the identification of neuroinvasive West Nile disease in a virus-specific IgM test performed on CSF [43].

Standard serologic testing can also be used diagnostically. Serum obtained from blood collected during the acute infection can be evaluated for the presence of pathogen-specific IgM and/or IgG antibody for Epstein-Barr virus, cytomegalovirus, parvovirus B19, human immunodeficiency virus,

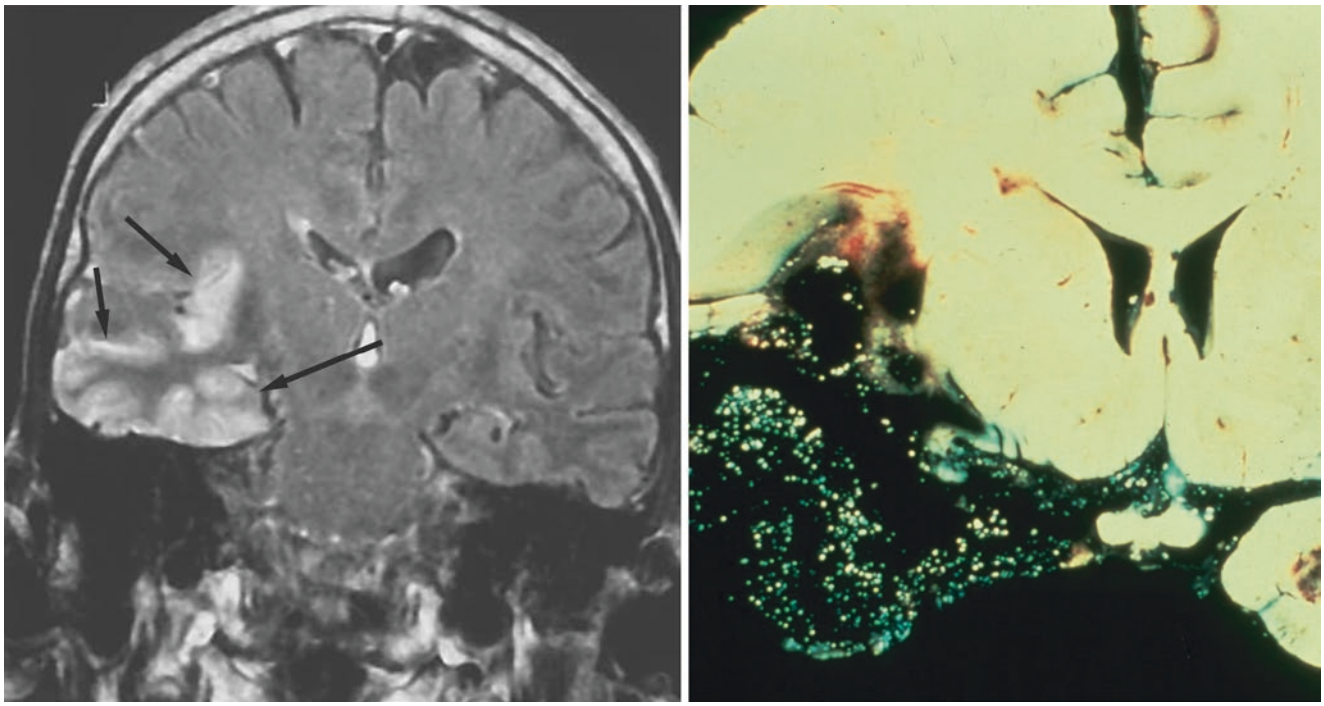

**Fig. 25.1** The gadolinium contrast-enhanced magnetic resonance image of the brain on the left is a coronal view showing extensive inflammatory changes and edema (*arrows*) in the right temporal lobe of a young adult patient presenting with fever, seizures, and altered level of consciousness alternating with bizarre, combative behavior. Cerebrospinal fluid tested positive for herpes simplex virus type 1 by polymerase chain reaction. Despite treatment with intravenous acyclovir, the patient died 4 days later. Autopsy revealed extensive areas of hemorrhagic necrosis involving the entire right temporal lobe, extending superiorly to the right parietal lobe and anteriorly into the frontal lobe. The image on the right shows a coronal section of the brain, as seen at autopsy, prepared from an anatomic position at approximately the same level as the magnetic resonance image on the left from 4 days earlier. (Image provided by Dr. Joseph Domachowske)

*Borrelia burgdorferi,* and many of the arboviruses. In some instances, acute and convalescent titers will be necessary. Serum samples that are collected early during the illness are archived until a convalescent sample becomes available 3–6 weeks later. In general, the serologic test result is considered positive if the antibody titers detected from the paired samples differ by fourfold or more.

Diagnostic testing performed on CSF and serologic testing performed on blood are important to establish the microbiologic diagnosis, but definitive results often require somewhat lengthy turnaround times. Clues that may help to predict the underlying cause of the infection while waiting for the definitive reports can sometimes be gleaned from the patterns of results already available from routine laboratory tests. A careful review of available results from complete blood counts, serum electrolytes, blood urea nitrogen creatinine, and hepatic transaminases may show patterns that support a particular etiology. The presence of leucopenia and/or thrombocytopenia suggests rickettsial infections, particularly in those patients with hyponatremia and modest elevations in serum transaminases. The presence of a significant atypical lymphocytosis in combination with mild hepatic transaminitis is highly suggestive of EBV infection. Peripheral blood eosinophilia is characteristic of parasitic infections, including those caused by migratory roundworms. Collecting a nasopharyngeal sample for rapid turnaround, multiplex PCR testing for respiratory pathogens can be considered. The detection of *M. pneumoniae*, adenoviruses, influenza viruses, and enteroviruses from the respiratory tract is, at best, indirect evidence that the central nervous system illness is caused by the same pathogen, so care should be taken to interpret the results in the proper context. Chest radiographs may also be indicated, depending on the history and physical examination findings. Pathogens with the potential to initiate infection in the respiratory tract with subsequent spread to the central nervous system include influenza viruses, adenoviruses, *M. tuberculosis*, *Nocardia* spp., *Histoplasma capsulatum*, and other dimorphic fungi.

Neuroimaging is an important diagnostic study that should be performed in patients with meningoencephalitis to help exclude noninfectious causes of their illness and to evaluate the extent of parenchymal brain involvement. Magnetic resonance imaging (MRI) of the brain is the preferred neuroimaging modality in the evaluation of meningoencephalitis. It is more sensitive than computed tomography (CT) for the detection of parenchymal disease, including demyelination. The use of CT scans is appropriate if MRI is unavailable or cannot be performed [28]. Some etiologies of meningoencephalitis have characteristic neuroimaging findings. For example, focal lesions in the basal ganglia, thalami, and brainstem are typical of arbovirus infection, while the presence of edema and hemorrhage in the frontotemporal lobes is most characteristic of infection with herpes simplex virus [44–46] (Fig. 25.1).

## 25.4 Infectious Causes of Meningoencephalitis: *Viruses*

### 25.4.1 Human Herpesviruses

Human herpesviruses are ubiquitous, globally distributed, DNA viruses which cause infection all year-round. Initial exposure to a human herpesvirus results in primary infection, which may be subclinical or symptomatic, followed by a period of latency. Since all herpesviruses establish latency, they have the potential to reactivate at a later time. Nine members of the *Herpesviridae* family are known to cause human infection. All nine have neurotropic potential, but some are much more likely than others to cause central nervous system infection. [▶ Call Out Box 25.3].

#### 25.4.1.1 Herpes Simplex Virus

Herpes simplex viruses (HSV) are among the leading causes of identified sporadic infectious meningoencephalitis worldwide [1, 2, 32, 47, 48]. There are two types of HSV: HSV-1 and HSV-2. Both virus types can cause primary infection and establish latency in the mucosal of the oropharynx or the genital tract. HSV-1 is the more usual cause of infection around the mouth and lips (cold sores), while HSV-2 accounts for a majority of genital HSV infections. Both HSV-1 and HSV-2 contribute to the overall burden central nervous system infection. While HSV-1 causes most cases of meningoencephalitis in immunocompetent adults, both HSV types contribute to disease seen in newborns.

HSV infection can be divided into neonatal disease and that occurring beyond the neonatal period. Neonates acquire HSV through contact with infected secretions, either during delivery or from symptomatic or asymptomatic shedding by a parent, sibling, or other caregiver during the immediate postnatal period. Infants born to mothers who experience a primary HSV infection close to the time of delivery are at the highest risk of acquiring neonatal HSV disease compared to those infants born to mothers with known recurrent genital herpes. Other factors associated with the perinatal transmission of herpes infection include maternal HSV antibody status, prolonged duration of ruptured membranes, and the use of fetal scalp monitoring electrodes [49]. Similarly, transmission of HSV to a susceptible person, beyond the neonatal period, occurs through close contact with an individual who is symptomatically or asymptomatically shedding the virus from their skin or mucosal membranes.

Individuals who are exposed to HSV become infected when the virus gains entry through injured skin or mucosal membranes. Primary infection may be subclinical, may be associated with fairly impressive signs and symptoms at the inoculation site, or may less commonly erupt as a severe systemic illness with or without involvement of the central nervous system. During the primary infection, the virus invades local sensory nerve endings, traveling retrograde along the axon to the sensory ganglion. As the host immune system controls the primary infection, virus in the sensory ganglion remains latent until reactivation. During virus reactivation, the virus migrates anterograde along the axon back to the original inoculation site on the skin or mucous membranes. HSV reactivation results in either symptomatic disease, as occurs with recurrent cold sores and recurrent genital herpes, or in asymptomatic virus shedding [49].

HSV meningoencephalitis is an uncommon complication of primary HSV infection. Presenting signs and symptoms include mental status changes, headaches, focal neurologic deficits, fever, and seizures [21, 31, 45, 46]. Complications include status epilepticus, intracranial hemorrhage, acute respiratory failure, cerebral edema, brainstem herniation, and death [21]. Neuroimaging and electroencephalogram (EEG) studies may reveal the typical temporal or frontotemporal lesions associated with HSV encephalitis (◘ Fig. 25.1), but any part of the brain can be involved [31, 45, 46].

The diagnosis of HSV meningoencephalitis is confirmed by performing an HSV-specific PCR-based assay on the patient's cerebrospinal fluid [50, 51]. HSV PCR assays are highly sensitive (~96%) and specific (~99%) for the diagnosis. Essentially all infected patients will have a positive HSV PCR test at the onset of their neurologic symptoms. PCR is so sensitive that testing remains positive even after 5 days of antiviral therapy. Before PCR-based testing became routinely available, a definitive diagnosis often depended on HSV-specific stains and cultures performed on tissue obtained from a brain biopsy [50–52]. Other antigen and antibody-based assays that were once used to aid in the diagnosis of HSV meningoencephalitis have likewise been replaced by PCR [51].

It is important to note that false negative PCR results can occur very early in disease; therefore, if clinical suspicion for HSV meningoencephalitis is high and the PCR result is negative, treatment with acyclovir should continue at least until a repeat cerebrospinal fluid sample is collected and tested 3–7 days later [43, 50, 53]. If the level of suspicion for HSV meningoencephalitis remains high despite repeat negative

**Call Out Box 25.3**

| Cause CNS infections in both healthy and immunocompromised patients | Cause CNS infection in immunocompromised patients only | Not typically associated with CNS infections |
|---|---|---|
| Herpes simplex virus type 1<br>Herpes simplex virus type 2<br>Epstein-Barr virus<br>Varicella zoster virus<br>Human herpes virus 6<br>Herpes B virus | Cytomegalovirus | Human herpes virus 7<br>Human herpes virus 8 |

PCR test results, some experts recommend that the patient should receive a full 21-day treatment course with intravenous acyclovir unless or until a logical alternative diagnosis is confirmed as the results of other diagnostic tests become available.

All PCR-confirmed cases of HSV meningoencephalitis should be treated with intravenous acyclovir for at least 21 days. Cerebrospinal fluid should be collected by repeat lumbar puncture performed near the end of therapy so that a posttreatment HSV PCR can be performed. If the posttreatment PCR result is still positive, antiviral therapy should be extended beyond 21 days [28].

Without treatment, 70% of patients with HSV meningoencephalitis will die from the infection. Even with appropriate treatment, HSV meningoencephalitis can be a devastating disease. Permanent neurological sequelae should be expected. Extensive brain injury leaves some patients completely dependent on others for care. Spasticity, with motor planning problems and other developmental issues are common sequelae in children. Lifelong neurocognitive problems such as memory impairment, personality and behavioral changes, and psychiatric conditions are not uncommon [43]. Factors that are associated with worse outcomes include age more than 30 years, a Glasgow Coma Score of less than 6 during the acute phase of the illness, symptoms for more than 4 days before antiviral therapy is initiated, and a positive cerebrospinal fluid HSV PCR at the end of therapy [28]. In an effort to reduce the morbidity and mortality associated with central nervous system HSV disease, intravenous acyclovir should be administered empirically to all patients with suspected meningoencephalitis until HSV infection has been ruled out.

Intravenous acyclovir is also used to treat perinatal HSV infections in newborns. Following treatment, all newborns remain at risk for central nervous system reactivation. Suppression of reactivation is achieved by administering oral acyclovir for 6 months starting immediately after the intravenous course of therapy has been completed. Oral acyclovir suppression of HSV reactivation is associated with improved neurodevelopmental outcomes [54]. In contrast, a large clinical trial found no improvement in the neuropsychological testing results of adults who received 3 months of oral valacyclovir suppression after completing a course of intravenous acyclovir [55].

#### 25.4.1.2 Varicella Zoster Virus

Varicella zoster virus (VZV) is a fairly common identified cause of meningoencephalitis. VZV infection results in two distinct clinical entities: varicella (chickenpox), seen with primary infection, and herpes zoster (shingles) seen with reactivation disease. Varicella epidemiology changed drastically after the introduction of varicella vaccination programs during the mid-1990s [56].

Varicella zoster virus is highly contagious. Transmission is airborne, similar to measles and smallpox. Aerosolized virus spreads from infected individuals to infect the respiratory mucosa of susceptible individuals with a very high attack rate [56]. Primary VZV infection in susceptible hosts causes varicella (chickenpox). The illness begins as a febrile respiratory infection. As the infection progresses, vesicles begin to appear on the skin. The rash is intensely itchy, typically starting on the scalp or at the hairline, moving to the trunk and then out to the extremities, sparing the palms and soles. When they first appear, the small vesicles sit on an erythematous base and contain clear fluid. Crops of vesicles turn to small pustules, eventually scabbing over as crops of new vesicles continue to appear. In 7–10 days, all vesicles have scabbed, and no new ones are formed. Varicella infection self-resolves for the majority of patients, at which time the virus remains latent in sensory ganglia. Reactivation of latent VZV results in herpes zoster (shingles) as a painful, burning, or tingling vesicular rash typically limited to a single dermatome. VZV meningoencephalitis can complicate either the primary infection or the reactivation illness.

VZV central nervous system disease can manifest as (a) acute cerebellar ataxia, a self-limiting process that occurs in children approximately 1–3 weeks after the onset of varicella infection and typically results in full recovery; (b) diffuse meningoencephalitis, a severe complication of VZV infection seen more commonly in adults that can lead to neurologic sequelae; or (c) aseptic meningitis. While initially thought to affect only immunocompromised patients, studies describing VZV central nervous system infection in immunocompetent patients have been reported [15, 16, 57].

The clinical presentation of VZV meningoencephalitis includes fever, headache, nausea, vomiting, altered mental status, and cranial nerve involvement, most commonly involving the seventh and eighth cranial nerve [15, 16, 58]. A cutaneous rash may or may not be present; thus, the absence of a rash does not exclude the possibility of central nervous system VZV infection [15, 16, 57, 58]. Neuroimaging may show diffuse encephalitis with vasculitis, ischemic stroke, demyelination, or swelling of the cerebral cortex, basal ganglia, or cerebellum [3, 28].

The diagnostic test of choice for VZV meningoencephalitis is virus-specific PCR performed on fluid from a vesicular skin lesion, saliva, or cerebrospinal fluid. This test will provide rapid and sensitive results for the detection of virus. VZV infection can also be diagnosed using antigen testing by direct immunofluorescence, detecting virus-specific antibodies in the cerebrospinal fluid, or through serologic testing, all of which have lower sensitivity and/or specificity compared to PCR-based assays [3, 28, 59, 60]. There is little utility in attempting viral culture for VZV. The virus is difficult to propagate in the laboratory even if the cell monolayers that support its growth are inoculated directly, at the bedside [59].

Currently, there are no clinical trials to guide the treatment of varicella encephalitis. However, based on the favorable safety profile of acyclovir and data suggesting that acyclovir treatment reduces symptoms and disease severity during primary varicella infection, intravenous acyclovir is recommended for the treatment patients with VZV menin-

goencephalitis [28, 60]. Ganciclovir can be used as an alternative agent. Corticosteroids can be considered as adjunctive therapy in patients with VZV CNS disease [28].

#### 25.4.1.3 Other Human Herpesviruses

Exposure to other human herpesviruses, including Epstein-Barr virus (EBV), cytomegalovirus (CMV), and human herpesvirus 6 (HHV-6), most commonly results in asymptomatic or subclinical infection, but these viruses have also been identified as causes of meningoencephalitis in both immunocompetent and immunocompromised patients. Meningoencephalitis caused by EBV infection can be associated with the unusual symptom of metamorphopsia. Metamorphopsia is described as visual perceptions (hallucinations) of three-dimensional, overlapping, colorful geometric shapes and figures that expand and shrink in size in one visual field. It's a very rare, bizarre complaint sometimes referred to as "Alice in Wonderland" syndrome that has also been described by some patients with vascular headaches.

The clinical presentation of meningoencephalitis caused by human herpesviruses includes fever, headache, photophobia, altered level of consciousness, seizures, confusion, hallucinations, and memory changes [61–63]. Neuroimaging may reveal involvement of the temporal lobe, corpus callosum, basal ganglia, thalamus, and/or periventricular areas [63–71]. The diagnosis of meningoencephalitis due to these human herpesviruses is made primarily through the use of virus-specific PCR assays performed on CSF [28]. The diagnosis of acute EBV infection is based on serologic testing, which includes the presence of EBV antiviral capsid antigen (VCA) IgM and IgG, Epstein-Barr nuclear antigen (EBNA), and the early antigen (EA). The presence of VCA IgM is indicative of acute or recent infection. The presence of EBNA in combination with a positive VCA IgM suggests recent infection over acute infection because the EBNA takes several weeks to months to appear. The presence of both the VCA IgG and EBNA reflects a past EBV infection.

There are no clear treatment guidelines for meningoencephalitis caused by EBV, CMV, or HHV6. However, the combination of ganciclovir and foscarnet has been used to treat HIV-infected patients with CMV encephalitis, with the understanding that therapeutic concentrations of these antivirals are unlikely to be achieved in the cerebrospinal fluid [28]. Since CMV infection typically happens during severe immunosuppression, reducing immunosuppressive therapy, if possible, should be a component of the therapeutic management [28].

#### 25.4.1.4 Herpes B Virus

Herpes B virus, a zoonotic virus endemic among macaque monkeys, is a known cause of meningoencephalitis among humans who are bitten or scratched by infected monkeys, typically in a research laboratory setting [72]. Symptoms, including fevers, lymphadenitis, and peripheral neuropathy, occur a few days to weeks after exposure, followed by the development of a destructive hemorrhagic meningoencephalitis. The diagnosis of herpes B virus infection includes serologic testing, PCR-based testing, and viral cultures from the wound. Treatment for individuals with herpes B central nervous system infection is intravenously administered ganciclovir. Prophylaxis of exposed individuals, including those who have been bitten or scratched by a macaque known to be seropositive for or shedding herpes B virus, or whose status is unknown, involves early wound cleaning and irrigating and a 14-day course of valacyclovir or acyclovir [72].

### 25.4.2 Picornaviruses

Enteroviruses and parechoviruses are non-enveloped, single-stranded RNA viruses in the *Picornaviridae* family [73, 74]. These viruses cause a wide spectrum of disease, from clinically asymptomatic infection to febrile illness with nonspecific rash and to aseptic meningitis (very common) and meningoencephalitis (rare). Enteroviruses, such as coxsackieviruses A and B; echoviruses 4, 5, 9, 11, 19, and 30; and enteroviruses 71, 75, 76, and 89, and human parechovirus 3 have all been implicated in sporadic and epidemic cases of meningoencephalitis, worldwide. Enterovirus 71, in particular, has been identified as an aggressive neurotropic virus causing outbreaks of life-threatening rhomboencephalitis [75]. Enterovirus and parechovirus infections are seen more commonly during the summer and fall months in temperate locations and year-round in the tropics. While these viruses infect individuals of all ages, the most common infections are seen in young children.

Transmission of enteroviruses and parechoviruses occurs through fecal-oral contamination or by contact with infected respiratory secretions. The initial viral replication occurs in the epithelial cells of the intestinal mucosa. The virus, then, crosses the intestinal cells to reach the lamina propria, where replication is more robust, eventually leading to viremia and secondary infection of the central nervous system [73]. Following primary infection, shedding of virus in upper respiratory secretions and feces can occur for weeks to months [74]. The most common manifestation of central nervous system disease is aseptic meningitis.

Patients with enterovirus or parechovirus meningoencephalitis present with the same non-specific signs and symptoms typically associated with the disease process, including fever, headache, vomiting, altered mental status, and focal neurologic deficits [16, 43, 76]. In addition, these patients may have associated symptoms of rash and diarrhea. Magnetic resonance images of patients with human parechovirus meningoencephalitis reveal inflammatory changes in the white matter, while images of those with enteroviral disease more typically show lesions in the medulla oblongata, pons, midbrain, and dentate nuclei of the cerebellum [76, 77]. These changes tend to be temporary, although long-term deficits have been described.

The preferred diagnostic test for enterovirus infection used to be isolation of virus through culture. However, with the advent of RT-PCR, with its improved sensitivity and specificity and a faster turn-around time for results, enterovirus-specific PCR assays from blood, CSF, and oropharyngeal or rectal swabs, are the new gold standard for the diagnosis of an enterovirus or parechovirus CNS infection [75].

There are currently no available antiviral treatment options for enterovirus or human parechovirus meningoencephalitis. Pleconaril, a viral capsid inhibitor with high oral bioavailability, has shown promise but remains unavailable. Immunoglobulin intravenous (IgIV) has been used anecdotally to treat patients with enteroviral or parechoviral meningoencephalitis, but evidence regarding treatment efficacy are lacking.

### 25.4.3 Arboviruses

Arboviruses, or viruses transmitted by arthropods (such as mosquitoes and ticks), include several small RNA viruses belonging to one of four families: *Togaviridae*, *Flaviviridae*, *Bunyaviridae*, and *Reoviridae* [78]. The arthropod vector acquires virus after feeding on an infected animal. The virus replicates in the arthropod, which then transmits infection when it bites a human. As arboviruses are dependent on their host vector's life cycle to cause human disease, these viruses vary in their geographic distribution and seasonality of infection.

#### 25.4.3.1 West NileVirus (WNV)

WNV, a virus in the *Flaviviridae* family found across the world, is now the leading cause of mosquito-borne viral meningoencephalitis in the United States [78]. It is transmitted primarily by the female *Culex* spp. mosquito, which acquires the virus from infected birds and then passes the virus onto humans during feeding. Transmission of WNV has also been documented to occur from blood transfusions, organ transplantations, and exposure to body fluids during delivery [17]. Infection during pregnancy can result in congenital infection with neurological sequelae in the newborn. It has been estimated that while 25% of those infected with WNV develop a febrile illness, only about 1% develop central nervous system involvement [17, 79]. Risk factors for the development of neuroinvasive disease include increasing age, male gender, non-white race, organ transplant recipients, and comorbid medical conditions, such as diabetes, hypertension, and cancer [80–82].

In symptomatic WNV infection, the clinical presentation includes a non-specific febrile illness with an associated maculopapular rash that appears around time of defervescence. Those who develop central nervous system involvement tend to do so during this phase of the infection. Neuroinvasive WNV manifests as either aseptic meningitis, meningoencephalitis, or flaccid paralysis. Cranial nerve palsies and movement disorders, such as tremors, myoclonus, and parkinsonism have been described among those diagnosed with WNV infection [83, 84]. Laboratory evaluation may show a mild leukocytosis, hyponatremia, cerebrospinal fluid pleocytosis, and elevated CSF protein concentrations. Magnetic resonance imaging may reveal lesions in the pons, basal ganglia, thalamus, brainstem, and cerebellum [17, 84]. The diagnosis of WNV central nervous system infection is made through the detection of IgM antibody in cerebrospinal fluid and serum. The majority of infected patients will have detectable IgM antibodies in their CSF during the first week of symptoms [17]. On the other hand, if initial IgM testing is negative, acute- and convalescent-phase serologic testing may aid in the diagnosis [17]. Currently, there is no antiviral therapy available for the treatment of severe WNV infection. The prognosis is variable for patients with neuroinvasive WNV infection. Those who present with aseptic meningitis are most likely to fully recover, and those who present with meningoencephalitis are at a higher risk for morbidity, including persistent movement disorders and cognitive deficits. A small subset of patients do not survive the infection.

#### 25.4.3.2 Eastern Equine Encephalitis (EEE) Virus

EEE, a virus in the *Togaviridae* family that is most commonly found in the western hemisphere, is transmitted by the *Culiseta melanura* mosquito. Interestingly, this mosquito does not usually bite humans, and people are generally infected by *Aedes* spp. or *Culex* spp. mosquitoes which act as bridging vectors between infected birds and humans [84]. Reports of EEE cases are very rare. In the United States, cases of EEE are typically seen during the summer and fall months [84].

Clinically, EEE infection may manifest as a non-specific febrile illness with headache, nausea, and vomiting, followed by either resolution or by the development of meningoencephalitis. Once neurologic symptoms develop, clinical deterioration occurs rapidly, and many cases are fatal. Laboratory evaluation may reveal leukocytosis, hyponatremia, cerebrospinal fluid pleocytosis with a neutrophil predominance, and elevated protein concentration. Magnetic resonance imaging may show lesions in the basal ganglia, thalamus, and brainstem [44]. The diagnosis of EEE meningoencephalitis can be confirmed by detecting EEE IgM in CSF, observing a fourfold rise in serum antibody titers collected during the acute and convalescent phases, or isolating EEE virus from the tissue, blood, or CSF. There is no treatment currently available for EEE infection. Mortality rates exceed 30% [85]. Patients who survive EEE meningoencephalitis are left with severe neurologic sequelae.

#### 25.4.3.3 St. Louis Encephalitis (SLE) Virus

SLE virus, a flavivirus transmitted by *Culex* spp. mosquitoes found widely throughout the Americas, was among the leading causes of arboviral meningoencephalitis in the United States until the arrival and spread of WNV. SLE infection is most common in summer and fall months during peak mosquito activity. Uncommon modes of transmission of infection also include solid organ transplantation and blood transfusions.

The clinical spectrum of SLE virus infection varies from asymptomatic infection, to a non-specific febrile illness, to

severe meningoencephalitis. Advancing age is associated with an increased risk of central nervous system involvement and is associated with higher mortality [86, 87]. SLE virus meningoencephalitis presents with high fevers, headache, and altered mental status. Tremors of the eyelids, lips, and extremities, cranial nerve palsy, cerebellar ataxia, and seizures can also be seen [84]. Associated clues typical of SLE infection include urinary frequency, urgency, and retention. Respiratory symptoms and acute flaccid paralysis may also accompany the illness [87]. Laboratory evaluation typically shows a mild leukocytosis, hyponatremia due to the syndrome of inappropriate antidiuretic hormone secretion, sterile pyuria, and/or elevated hepatic transaminases and creatinine kinase. CSF pleocytosis with a lymphocytic predominance and elevated protein concentration are likely to be present. Neuroimaging is often normal.

The diagnosis of SLE virus meningoencephalitis is presumed by the presence of virus-specific IgM in the serum or CSF, although these antibodies may cross-react with West Nile virus antibodies. Paired acute and convalescent SLE virus antibody titers that demonstrate a fourfold rise or more is diagnostic of infection. Isolation of virus from the blood or cerebrospinal fluid is very difficult and associated with a low yield. There is currently no available treatment for SLE meningoencephalitis; however, a small pilot study suggested that early use of interferon-alpha2b may reduce the severity and complications of SLE meningoencephalitis [88]. While recovery from acute SLE virus infection can occur in the first 2 weeks, neurocognitive deficits, including gait imbalances, neuropsychiatric symptoms, and tremors, may persist.

#### 25.4.3.4 La Crosse Virus

La Crosse virus, a member of the *Bunyaviridae* family transmitted by the *Aedes triseriatus* mosquito, is the most common and most pathogenic of the California encephalitis group viruses. Infection is most commonly seen in school-aged children during the summer months, when the mosquito activity peaks.

The clinical presentation of La Crosse virus CNS infection includes fevers, headache, vomiting, seizures, alerted mental status, or focal neurologic deficits. Increased intracranial pressure leading to herniation and death has been described [89, 90]. The laboratory evaluation may reveal hyponatremia, leukocytosis, and CSF pleocytosis, while neuroimaging will likely show generalized cerebral edema with focal areas of gadolinium enhancement [89]. There are no currently available treatment options for La Crosse virus infections.

#### 25.4.3.5 Rabies

Rabies virus, a Lyssavirus in the *Rhabdoviridae* family, is a zoonotic infection found worldwide that is responsible for the deaths of 55,000 people annually. Most deaths occur in developing countries where there is a lack of rabies control among domesticated animals. Transmission of infection occurs through the bite of an infected animal, particularly dogs, raccoons, skunks, bats, or foxes. Virus transmission can also occur from inhaling contaminated aerosols while exploring caves or from accidental occupational exposure in the laboratory. Rabies virus has also been transmitted from an infected donor during organ transplantation [91, 92].

The incubation period for rabies averages between 1 and 3 months but can be several years. Clinical symptoms of rabies infection start with a non-specific prodrome, including low-grade fevers, malaise, and anorexia. The prodrome is then followed by either an encephalopathic phase, which includes progressively worsening altered mental status, autonomic instability, dysphagia, hydrophobia, and agitation, or a paralysis phase, evident by an ascending paralysis similar to Guillain-Barre syndrome [91, 93]. The progression of disease almost always results in death within a few weeks of symptom onset.

Diagnostic testing for rabies infection must come from multiple sources: a saliva sample for virus isolation and/or reverse-transcription PCR, serum and CSF for rabies antibodies, a skin biopsy including hair follicles from the nape of the neck for rabies antigen detection by direct fluorescent antibody testing, and corneal impressions for rabies antigen detection by direct fluorescent antibody testing. There is currently no known effective therapy for rabies infection once symptoms develop; however rabies treatment protocols continue to explored systematically using variations of the Milwaukee protocol.

The best strategies for preventing the development of rabies infection include both pre- and postexposure prophylaxis. Pre-exposure rabies prophylaxis is indicated for those individuals who are at high risk for exposure, including veterinarians and lab workers, those who work with rabies virus or rabid animals, and international travelers who may come into contact with rabid animals. Active vaccination of these at-risk groups, with regular booster doses for those who continue to be at risk, is recommended. Postexposure rabies prophylaxis, including rabies vaccine and rabies immunoglobulin (RIG), is indicated for those individuals who have been exposed to an animal known or possibly infected with rabies virus.

## 25.5 Infectious Causes of Meningoencephalitis: Bacteria

### 25.5.1 *Bartonella henselae*

This fastidious Gram-negative bacillus is responsible for most cases of cat-scratch fever, an illness that is occasionally associated with central nervous system involvement and does not always cause fever. Despite the occasional nature of the complication, *Bartonella henselae* is the most common cause of *bacterial* meningoencephalitis [35]. *B. henselae* infect the cat flea, *Ctenocephalides felis*, which transmits infection from cat to cat when it feeds. Humans most commonly acquire infection after being scratched by an infected, asymptomatic kitten. Perhaps a better name for the illness would be "kitten scratch disease." Infection is sometimes transmitted through bites or via mucosal contact with contaminated flea feces. Puppies and adult cats and dogs can also be sources of infection.

Cat-scratch disease (the most widely accepted medical term for this illness) begins with the appearance of a papule at the site of inoculation. Lymphadenopathy develops in the local or regional draining lymph nodes, often persisting for several weeks. On physical examination, the inflamed lymph node can feel unusually hard raising concern for possible malignancy. Fevers are not always present, but ironically, cat-scratch disease is one of the most common causes of prolonged, unexplained fevers in children.

Atypical manifestations of cat-scratch disease include hepatosplenic involvement, retinitis, endocarditis, and meningoencephalitis. Meningoencephalitis presents abruptly with fevers and seizures between 1 and 6 weeks after the onset of lymphadenopathy [35]. Neuroimaging study results are often normal but may show subtle non-specific abnormalities. Acute and convalescent antibody titers are used to make the diagnosis of cat-scratch disease. If the acute titer is already markedly elevated in a patient with illness manifestations that are consistent with cat-scratch disease, a convalescent sample is unnecessary. Treatment of cat-scratch disease meningoencephalitis is supportive. Treatment with antibiotics, including doxycycline or azithromycin, with or without the addition of rifampin, may speed recovery [28]. The prognosis is excellent. The vast majority of patients recover without sequelae within 2 weeks or less.

### 25.5.2 *Mycoplasma pneumoniae*

*M. pneumoniae*, a fastidious bacterium lacking a cell wall, is ubiquitous, causing infection year-round, worldwide. The organism is a leading cause of pneumonia among school-aged children and young adults. Respiratory infection can be associated with various immunological phenomenon including the production of cold agglutinin antibodies, sometimes with evidence for an associated autoimmune hemolytic anemia. Infection with *M. pneumoniae* is also one of the most common known infectious triggers for the development of Stevens-Johnsons syndrome. Meningoencephalitis has been described as another, much less common complication of *M. pneumoniae* infection. Transmission of *M. pneumoniae* occurs through contact with the respiratory droplets of an infected individual.

Patients with *M. pneumoniae* meningoencephalitis present with fevers, altered mental status, seizures, and/or focal neurologic deficits [94]. Results of neuroimaging studies are usually normal. In contrast, electroencephalogram (EEG) studies are usually abnormal showing either diffuse slowing or identifying focal abnormalities [94]. The failure to reliably and convincingly demonstrate the presence of *M. pneumoniae* in cerebrospinal fluid via culture or PCR under these circumstances and the proclivity of the organism to trigger unusual immunologic events have led to the suggestion that meningoencephalitis may be a noninfectious, immune-mediated complication of the pulmonary infection. Treatment options for *M. pneumoniae* infection include azithromycin, doxycycline, or fluoroquinolones [28].

### 25.5.3 *Borrelia burgdorferi*

*Borrelia burgdorferi* is the bacterium that causes Lyme disease. The most common central nervous system manifestations of Lyme disease occur during the early disseminated phase of infection and include aseptic meningitis and seventh cranial nerve palsy, among others. Meningoencephalitis is a rare but very serious manifestation of late Lyme disease. Comprehensive discussions on all aspects of Lyme disease are included in ▶ Chap. 32. Additional information about central nervous system manifestations can be found in ▶ Chap. 22.

## 25.6 Amoebic Meningoencephalitis

Primary amoebic meningoencephalitis (PAM) is caused by the free-living amoeba, *Naegleria fowleri*. This parasitic disease causes a devastating, rapidly fatal central nervous system infection. *N. fowler* is most commonly found in warm bodies of freshwater, including lakes, rivers, and hot springs. Infections are most commonly reported from the southern United States. Transmission occurs when water contaminated with the parasite enters the nasal passages while the head is partially or completely submerged, as with swimming [95]. Amoebae migrate in retrograde fashion along the olfactory nerves to the olfactory bulb directly into the brain.

Patients with PAM present similarly to those with bacterial meningitis, with fevers, bifrontal or temporal headaches, nausea, vomiting, and nuchal rigidity. These early signs and symptoms are followed by progressive neurologic dysfunction with altered mental status, seizures, behavioral changes, and cranial nerve palsies [95, 96]. Results from neuroimaging and routing laboratory testing are non-specific. The diagnosis of PAM is made primarily through real-time PCR assays of performed on cerebrospinal fluid. Direct visualization on wet mount, or with staining techniques, is also possible. Cultures can also be requested. CSF is incubated on a lawn of *E. coli* bacteria. As the amoebae reproduce, they consume the bacteria leaving behind trails that can be visualized microscopically.

The mortality rate for PAM exceeds 95%. Optimal treatment is unknown; however liposomal amphotericin B is a recommended therapy when this disease process is suspected [28].

Granulomatous amebic meningoencephalitis, caused by either *Acanthamoeba* species or *Balamuthia mandrillaris*, is a chronic infection that progresses much more slowly than PAM, leading to death in weeks to months following the first signs of infection. These free-living amoebae are found worldwide in freshwater, soil, and dust. Infection occurs after inhalation of amebic cysts that are present in the water or following contact with contaminated soil [96].

Patients with granulomatous amebic meningoencephalitis present with gradual onset of behavioral changes, vision loss, ataxia, headaches, and seizures over the course of weeks to months [96]. Findings on neuroimaging are non-specific and of limited value in making diagnosis. The diagnostic tests

of choice are organism-specific real-time PCR assays performed on cerebrospinal fluid. Treatment options for *Acanthamoeba* spp. infection include various combinations of trimethoprim-sulfamethoxazole, miltefosine rifampin, fluconazole, pentamidine, and sulfadiazine [28].

## 25.7 Special Populations

Immunodeficient patients are susceptible to the development of central nervous system infections from a variety of causes. For example, patients with underlying agammaglobulinemia and CD40 ligand deficiency are at risk for developing chronic enteroviral meningoencephalitis. The chronic nature of the infection results in a gradual loss of developmental milestones with progressive neurologic dysfunction over the course of several months to years before causing the patient's death. A second example includes patients with primary immune deficiencies involving the toll-like receptor (TLR) 3 signaling pathway. Patients with these TLR3-associated signaling deficiencies are at an increased risk for the development of recurrent HSV meningoencephalitis [97].

**Case Study**

**Practical Example**

*A previously healthy 5-year-old male presents to the Emergency Department with a 2-day history of fevers and headaches when he developed seizures and altered mental status. After securing the airway, a diagnostic evaluation was initiated including a complete blood count, electrolytes, creatinine, hepatic transaminases, blood cultures, a nasopharyngeal swap for respiratory virus studies, and complete cerebrospinal fluid analysis. Which of the following is the next appropriate step in the management of this patient?*

A. Magnetic resonance imaging (MRI) of the brain
B. Electroencephalogram (EEG)
C. Intravenous administration of acyclovir
D. Computed tomography (CT) scan of the brain and spine

(C) In the management of patients with meningoencephalitis, it is important to treat for herpes simplex virus infection as soon as the diagnosis is suspected to improve outcomes associated with disease process. Following the administration of intravenous acyclovir, MR imaging of the brain will aid in determining the severity of disease, and EEG studies will assist in the evaluation of the persistent seizure activity.

## 25.8 Exercises

Please refer to the supplementary information section for answers to these exercises.

1. Which of the following causes of meningoencephalitis is not an arbovirus?
   a. West Nile virus
   b. Powassan virus
   c. Rabies virus
   d. La Crosse virus

2. List the vaccine-preventable causes of meningoencephalitis.

3. Match the clinical symptom or exposure with associated etiology of meningoencephalitis.

| Pathogen | Characteristic finding |
|---|---|
| 1. Warm freshwater swimming | A. St Louis encephalitis virus |
| 2. Hydrophobia | B. Varicella zoster virus |
| 3. Urinary symptoms | C. Herpes B virus |
| 4. Cranial nerve involvement | D. *Naegleria fowleri* |
| 5. Macaques | E. Rabies virus |

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# Toxin-Mediated Diseases, Bloodstream Infections and Their Complications

Contents

# Tetanus, Diphtheria, and Botulism

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**Learning Objectives**

- To learn the etiologic agent/s, transmission, pathophysiology, and epidemiologic characteristics associated with tetanus, diphtheria, and botulism.
- To understand the clinical presentations, approach in the diagnosis of tetanus, diphtheria, and botulism as well as the various differential diagnoses.
- To describe the different complications, treatment regimens, and prevention of tetanus, diphtheria, and botulism.

## 26.1 Tetanus

### 26.1.1 Introduction to the Problem

There are varying clinical presentations of tetanus, and one of the most common symptoms of this infection is tightening of the jaw or "lockjaw" [1]. This is a neurologic disease presenting as severe spasm of the muscles and trismus which includes risus sardonicus (Fig. 26.1) [2, 3]. In severe cases, patients may show symptoms of painful muscle stiffness all over the body [1] progressing to opisthotonic posturing (Fig. 26.2) [3, 4].

### 26.1.2 Definitions

**Lockjaw** - or trismus due to tightening of the muscles of the jaw [1].

**Risus sardonicus** - or "sarcastic smile" associated with muscle spasm [4].

**Opisthotonus** - is one of the most significant presentations of generalized tetanus manifesting as arching of the back resembling decorticate posturing [4].

### 26.1.3 Basic Concepts

Tetanus is caused by a neurotoxin produced by *Clostridium tetani*, an obligately anaerobic, large Gram-positive rod that produces terminal spores (Fig. 26.3) [3]. The organism and its spores can be isolated from a variety of sources including soil and the intestinal contents of numerous animal species. The spores are extremely stable in the environment, retaining the ability to germinate and cause disease indefinitely. They withstand exposure to ethanol, phenol, or formalin but can be rendered noninfectious by iodine, glutaraldehyde, hydrogen peroxide, or autoclaving at 121 °C for 15 min. A potent neurotoxin, referred to as tetanospasmin, is elaborated at the site of infection and rapidly binds to neural tissue causing a characteristic paralysis with tonic spasms [5].

Tetanus infections can result from spore contamination of deep-tissue puncture wounds, lacerations, or crush injuries [6]. Fecal contamination of the umbilical cord has been the source of *C. tetani* infection in some cases of neonatal tetanus. Cephalic tetanus associated with suppurative otitis media has been reported [7] (▶ Box 26.1). The conditions in a wound are particularly well suited to the bacteria's anaerobic requirements. In addition, tetanolysin, an exotoxin produced by *C. tetani*, may damage tissue surrounding an infection, further optimizing growth conditions within the wound [8].

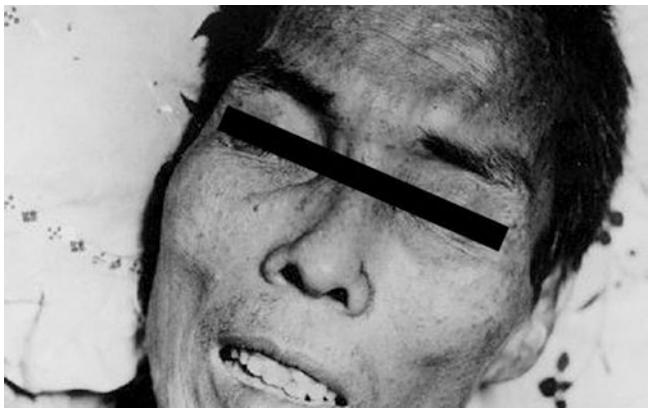


**Fig. 26.1** Spasm of the facial muscles in a patient with tetanus. (Courtesy of Centers for Disease Control and Prevention/ AFIP/C. Farmer)

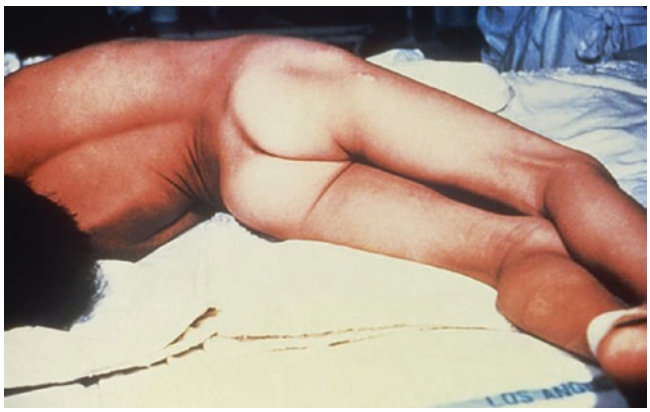


**Fig. 26.2** A patient with generalized tetanus presenting with arching of the back called opisthotonic posturing. (Courtesy of Centers for Disease Control and Prevention)

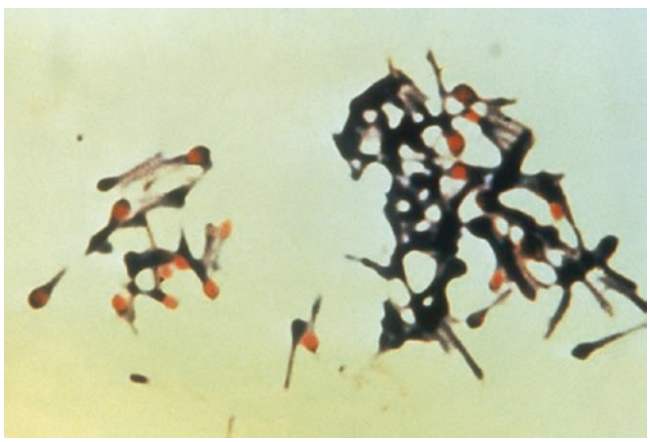
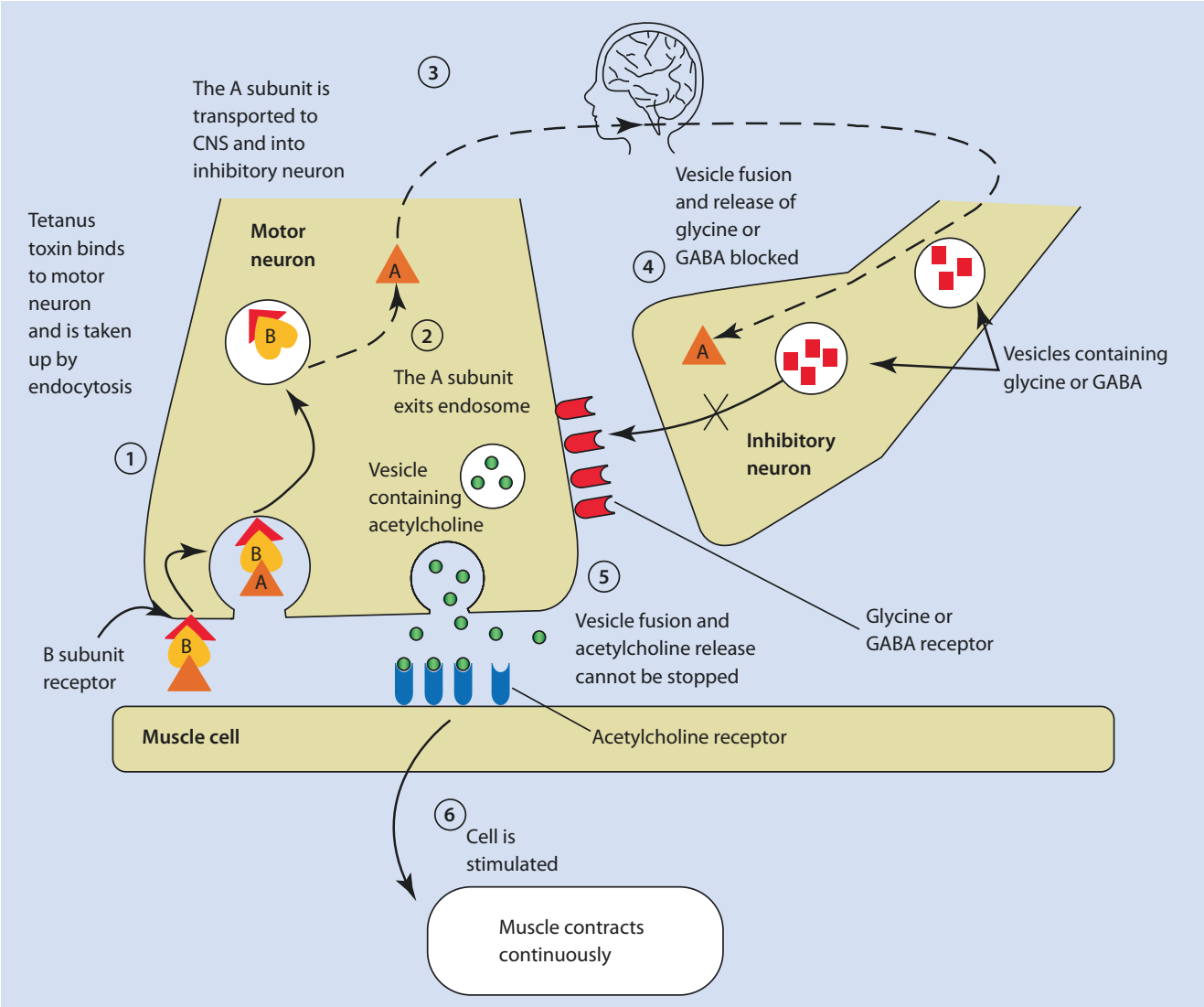


**Fig. 26.3** The micrograph shows the terminal spores produced by *Clostridium tetani*. (Courtesy of Centers for Disease Control and Prevention/Dr. Holdeman)

The clostridial toxins that produce both tetanus and botulism are similar in structure and function despite their differing clinical disease presentations. As with botulinum toxin, tetanus neurotoxin is synthesized as a single, inactive polypeptide chain which is cleaved by a bacterial protease to produce an active form consisting of a heavy chain and a light chain that remain connected [9]. The heavy chain binds to the presynaptic terminals of lower motor neurons, while the light chain enters the neuronal cell cytoplasm [10]. Tetanus toxin is an enzyme that initially targets proteins necessary for the release of neurotransmitters [9]. The initial symptom associated with *C. tetani* infection may therefore be flaccid paralysis caused by interference with vesicular release of acetylcholine at the neuromuscular junction just as it occurs with botulinum toxin [11]. However, unlike botulinum toxin, tetanus toxin undergoes retrograde transport in the axons to finally reach the neurons in the spinal cord and brain stem. The toxin targets inhibitory neurons that release the neurotransmitters glycine and GABA (γ-amino-η-butyric acid) [5]. Without release of these inhibitory signals, there is hyperactivity of the motor neurons and increased muscle activity in the form of rigidity and spasms. ◘ Figure 26.4 depicts the putative mechanism on how tetanus toxin mediates muscle spasms.

**Box 26.1 Clinical History Increasing Index of Suspicion for Tetanus** [1, 4]

- Burns
- Crush injuries
- Injuries with dead tissues
- Intravenous drug use
- Minor surgical procedures or rectal/vaginal instrumentation
- Puncture wounds from a nail or recent needle injection
- Wounds contaminated with feces, dirt, saliva




◘ **Fig. 26.4** Graphical illustration of the putative mechanism on how tetanus toxin mediates muscle spasms. (Courtesy of Mary George PhD, D(ABMM))

**Box 26.2 Signs and Symptoms Associated with Tetanus**

- Difficulty swallowing
- Fever and sweating
- Headache
- Jaw cramping
- Labile blood pressure and tachycardia
- Painful muscle stiffness of the body
- Sudden involuntary muscle tightening or muscle spasms

**Box 26.3 Overlapping Clinical Forms of Tetanus**

- **Cephalic tetanus** – impairment of cranial nerves due to decreased neuromuscular transmission associated with the infected wounds around the neck and head
- **Generalized tetanus** – the most common presentation of tetanus is a neurologic disease presenting as lockjaw, risus sardonicus, and severe muscle spasms with the involvement of the paraspinal muscles; some patients may manifest with opisthotonic spasm
- **Localized tetanus** – localized pain then weakness around the wound progressing to localized muscle spasms or rigidity
- **Neonatal tetanus** – a generalized tetanus in newborn infants due to absence of protective maternal immunity following infection of the umbilical stump after delivery outside the healthcare environment or from cultural practices that includes application of dirt or cow dung to the umbilical stump

The incubation period – time from exposure to disease – ranges from 3 days to 3 weeks most presenting within a week. Some occur sooner in those with heavily contaminated wounds and more severe disease presentation [1, 2].

The onset of tetanus is gradual, presenting over 1 day to 1 week then progressing to painful generalized muscle spasm that is usually aggravated by external stimuli [2]. ▶ Box 26.2 shows the different symptoms associated with tetanus [1, 2].

There are four overlapping clinical forms of tetanus – cephalic, generalized, local, and neonatal (▶ Box 26.3) [2, 4].

Tetanus is a clinical diagnosis; however, there are several differential diagnoses that need to be ruled out which include adverse drug reactions (phenothiazine reaction, strychnine poisoning), hypocalcemic tetany, meningitis, encephalitis, seizures, rabies, and conversion disorder [2, 4].

There is no specific diagnostic test for tetanus, and obtaining a wound culture for *C. tetani* is associated with poor yield. A negative wound culture does not rule out tetanus. Further, the presence of protective tetanus antibody concentration does not rule the diagnosis if the history and clinical presentation are suggestive of tetanus [2]. Laboratory tests are helpful to rule out other diseases since tetanus is a clinical diagnosis [4].

Tetanus is a medical emergency requiring hospital admission [12]. Eradication of *C. tetani*, neutralization of tetanus toxins, and supportive care remain the cornerstone in the management and care of patients with tetanus [4]. Intravenous metronidazole (PO if tolerating feeds) is the antimicrobial agent of choice in decreasing the vegetative forms of *C. tetani*, and parenteral penicillin G is an alternative agent. Human tetanus immune globulin (TIG) is recommended for neutralization of tetanus toxins, and immune globulin intravenous (IGIV) may be used if TIG is not available [2]. Local wound care, muscle relaxation, sedation, decrease of unnecessary external stimuli, and nutritional supports constitute the supportive care of patients with tetanus [4]. ◘ Table 26.1 describes the need for tetanus prophylaxis using tetanus toxoid with or without TIG depending on the history of immunization with tetanus toxoid and the nature of the wound [12].

▶ Box 26.4 shows the list of complications associated with tetanus [4, 12].

**◘ Table 26.1** Tetanus prophylaxis in routine wound management

| History of tetanus toxoid-containing vaccines | Clean, minor wound | | All other wounds[a] | |
|---|---|---|---|---|
| | DTaP, Tdap, Td[b] | TIG[c] | DTaP, Tdap, Td[b] | TIG[c] |
| <3 doses or unknown | Yes | No | Yes | Yes |
| ≥3 doses or unknown | No[d] | No | No[e] | No |

[a]For example, avulsions or wounds associated with burns, crushing, frostbite, and from missiles, puncture wounds, and wounds contaminated with dirt/soil, feces, and saliva
[b]DTaP = diphtheria and tetanus toxoids and acellular pertussis vaccine, recommended for children <7 years old; Tdap = tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis, preferred to Td for those ≥11 years and have not received Tdap; Td = tetanus and diphtheria toxoids; TIG = tetanus immune globulin
[c]TIG 250 IU intramuscularly for prophylaxis
[d]Yes, if ≥10 years from the last dose of tetanus toxoid-containing vaccine
[e]Yes, if ≥5 years from the last dose of tetanus toxoid-containing vaccine

**Box 26.4 Complications of Tetanus**

- Acute renal failure
- Aspiration pneumonia and respiratory compromise
- Cardiomyopathy
- Death
- Fractures
- Hypertension
- Hypoxic cerebral injury
- Laryngospasm
- Nosocomial infections
- Phrenic nerve and laryngeal nerve palsy
- Psychologic
- Pulmonary embolism
- Myositis and rhabdomyolysis

Primary immunization with tetanus toxoid-containing vaccines followed by booster doses remains the best way to prevent tetanus [4]. The CDC website contains the updated recommendations on tetanus toxoid-containing vaccines for children, adolescents, pregnant women, and adults which is available at ► https://www.cdc.gov/vaccines/vpd/dtap-tdap-td/hcp/recommendations.html. It also provides useful information on vaccinations of healthcare personnel, catch-up guidance for children 4 months through 18 years, as well as contraindications and precautions.

**Case Study**

**Practical Example**

An 18-year-old male is being evaluated at the local emergency room for a crushing injury on his right hand after he was thrown out of the car as a passenger during a motor vehicular accident. His right hand was crushed in between rocks and soaked in murky ditch water. He is admitted for surgical repair of his right hand and antibiotic prophylaxis administered for 3 days with piperacillin-tazobactam for empiric coverage against organisms from the dirty water. Further review of his medical record showed that he has not received any immunizations. Based on tetanus prophylaxis in routine wound management found in ◘ Table 26.1, you will administer Tdap vaccine and tetanus immune globulin to prevent tetanus.

### 26.1.4 Exercises

Please refer to the supplementary information section for answers to these exercises.

1. Identify the different risk factors associated in the transmission and exposure to tetanus infection.
2. Name the various symptoms and clinical presentation of tetanus.
3. Ask the director of the Microbiology Lab if they have photo micrographs on file of the *C. tetani* bacteria showing its characteristic terminal spore. The Centers for Disease Control and Prevention's website has a repository of pictures depicting the terminal spore of *C. tetani*.
4. Describe the overlapping clinical forms of tetanus and list the differential diagnoses for tetanus.
5. Discuss the cornerstone of management and complications of patients with tetanus.

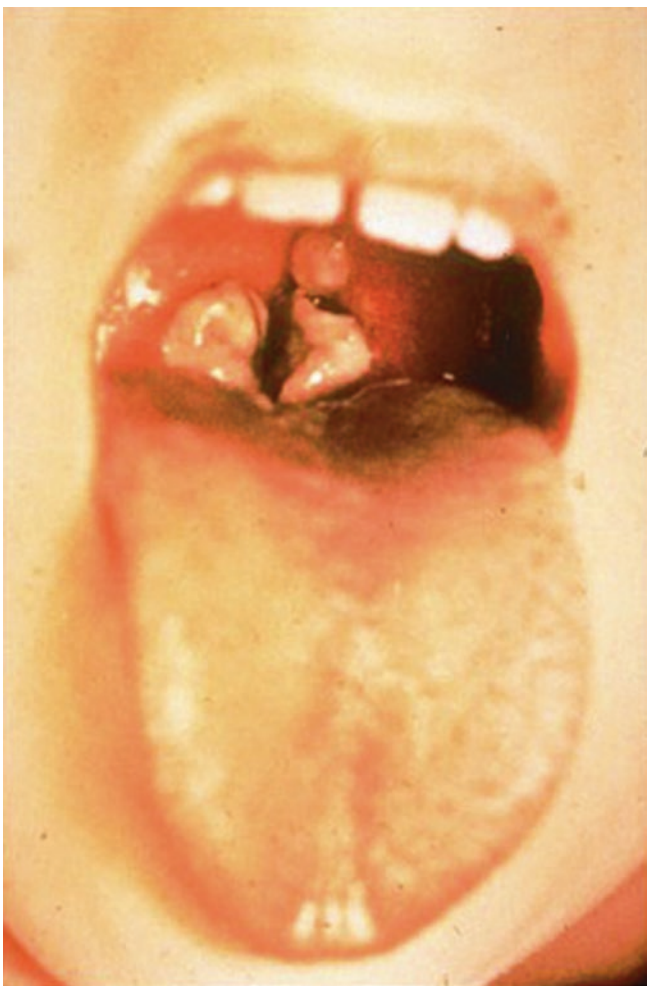
### 26.1.5 Summary

Tetanus is a neurologic disease presenting with localized or generalized muscle spasms resulting from *C. tetani* spore contamination of deep-tissue injuries. It remains a clinical diagnosis, and medical providers should have high index of suspicion if the history and clinical presentations are suggestive of tetanus. Tetanus is a medical emergency and antimicrobial therapy to eradicate *C. tetani*, neutralization of tetanus toxins and supportive care remain the cornerstone in the management and care of tetanus. Primary immunization with tetanus toxoid-containing vaccines followed by booster doses remains the best way to prevent tetanus.

## 26.2 Diphtheria

### 26.2.1 Introduction to the Problem

Respiratory tract diphtheria may occur as a membranous pharyngitis (◘ Fig. 26.5) [13] presenting with bloody nasal discharge, and in severe cases, some patients develop "bull neck" (◘ Fig. 26.6) [13] due to cervical lymphadenitis with extensive neck swelling [14]. Less commonly diphtheria may occur as a non-healing ulcer or cutaneous diphtheria (◘ Fig. 26.7) [13, 14].



◘ **Fig. 26.5** Pseudomembrane seen in a patient with respiratory diphtheria due to diphtheria toxin that triggers the production of a necrotic, coagulated mass of fibrin, leukocytes, dead respiratory epithelial cells, and bacteria. (Courtesy of Centers for Disease Control and Prevention)

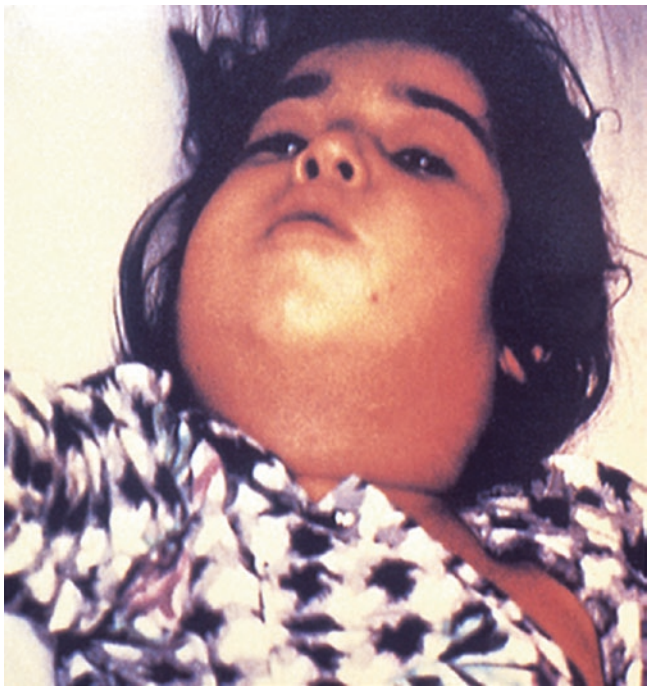


**Fig. 26.6** A young child with severe diphtheria presenting with characteristic extensive swelling of the neck referred to as "bull neck." Courtesy of Centers for Disease Control and Prevention

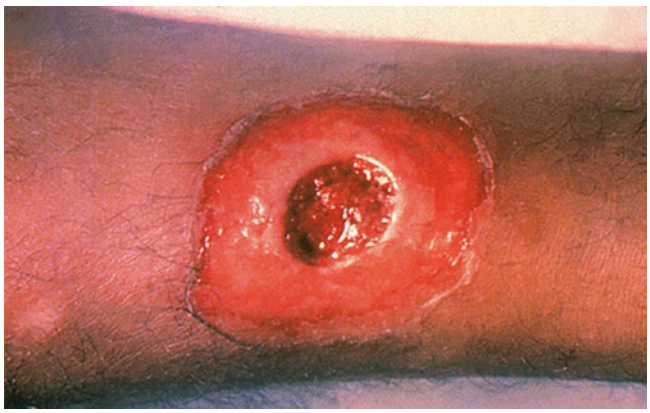


**Fig. 26.7** Cutaneous diphtheria in the lower extremity. (Courtesy of Centers for Disease Control and Prevention)

## 26.2.2 Definitions

**Pseudomembrane** - is a local inflammatory reaction induced by bacteria that is dense and adherent in the superficial layer of the skin or respiratory mucosa due to diphtheria toxin that triggers the production of a necrotic, coagulated mass of fibrin, leukocytes, dead respiratory epithelial cells, and bacteria.

**Bull neck** - is a sign of severe disease associated with diphtheria due to extensive neck swelling with cervical lymphadenitis [14].

## 26.2.3 Basic Concepts

*Corynebacterium diphtheriae* is the causative agent of diphtheria. First isolated in the laboratory in pure culture by Loeffler in 1884, *Corynebacterium diphtheriae* is an aerobic, Gram-positive, pleomorphic, nonspore-forming rod [15]. Its name is derived from the Greek words korynee or "club," referring to its clubbed ends (Fig. 26.8) [13], and diphtheria, meaning "leather hide" in reference to the leathery pharyngeal membrane seen with this illness (Fig. 26.5). The major virulence factor related to this bacterium is a potent exotoxin which inhibits protein synthesis in mammalian cells. Exotoxin production depends on the presence of a bacteriophage which carries the gene encoding for toxin (*tox*) [16]. Once inside the bacterium, the bacteriophages' circular DNA integrates into the host bacteria's genetic material as a prophage with the result that the bacterial cell now can express the gene necessary for synthesis of the toxin. Strains of *C. diphtheriae* lacking bacteriophage do not produce toxin. Strains of *C. ulcerans* and *C. pseudotuberculosis* can also carry this phage and can produce diphtheria-like illness [17].

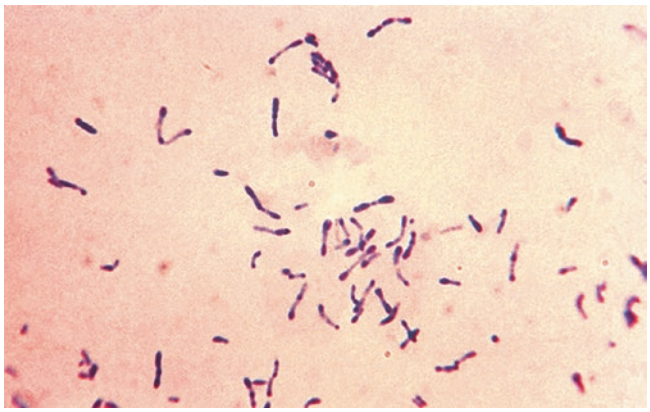


**Fig. 26.8** Photomicrograph of *Corynebacterium diphtheriae* showing its clubbed ends. (Courtesy of Centers for Disease Control and Prevention/Dr. P.B. Smith)

Diphtheria toxin has two segments. The B segment of the toxin binds to specific receptors on susceptible human cells, while segment A is the active component of the toxin. After proteolytic cleavage of the bound toxin molecule, segment A enters the cytoplasm of the human cell and catalyzes inactivation of tRNA translocase (elongation factor 2). Loss of this enzyme prevents the interaction of mRNA and tRNA and stops further addition of amino acids to developing polypeptide chains thus stopping protein synthesis (Fig. 26.9) [18]. The toxin affects all cells, but the most prominent effects are on the cells of the heart (myocarditis), nerves (demyelination), and kidneys (tubular necrosis). Within the first few days of respiratory tract infection, the toxin triggers the production of a necrotic, coagulated mass of fibrin, leukocytes, dead respiratory epithelial cells, and bacteria (pseudomembrane; Fig. 26.5) [13] along with underlying soft tissue swelling and cervical lymphadenitis (Fig. 26.6). Skin infection is characterized by chronic non-healing ulcers with a membrane (Fig. 26.7) [13]. There is little or no pain associated with these nonprogressive lesions that are only rarely associated with signs of systemic intoxication [19].

Humans are the only known reservoir for *C. diphtheriae*, and healthy individuals can carry the bacterium asymptomatically in the throat. Primary modes of spread are airborne

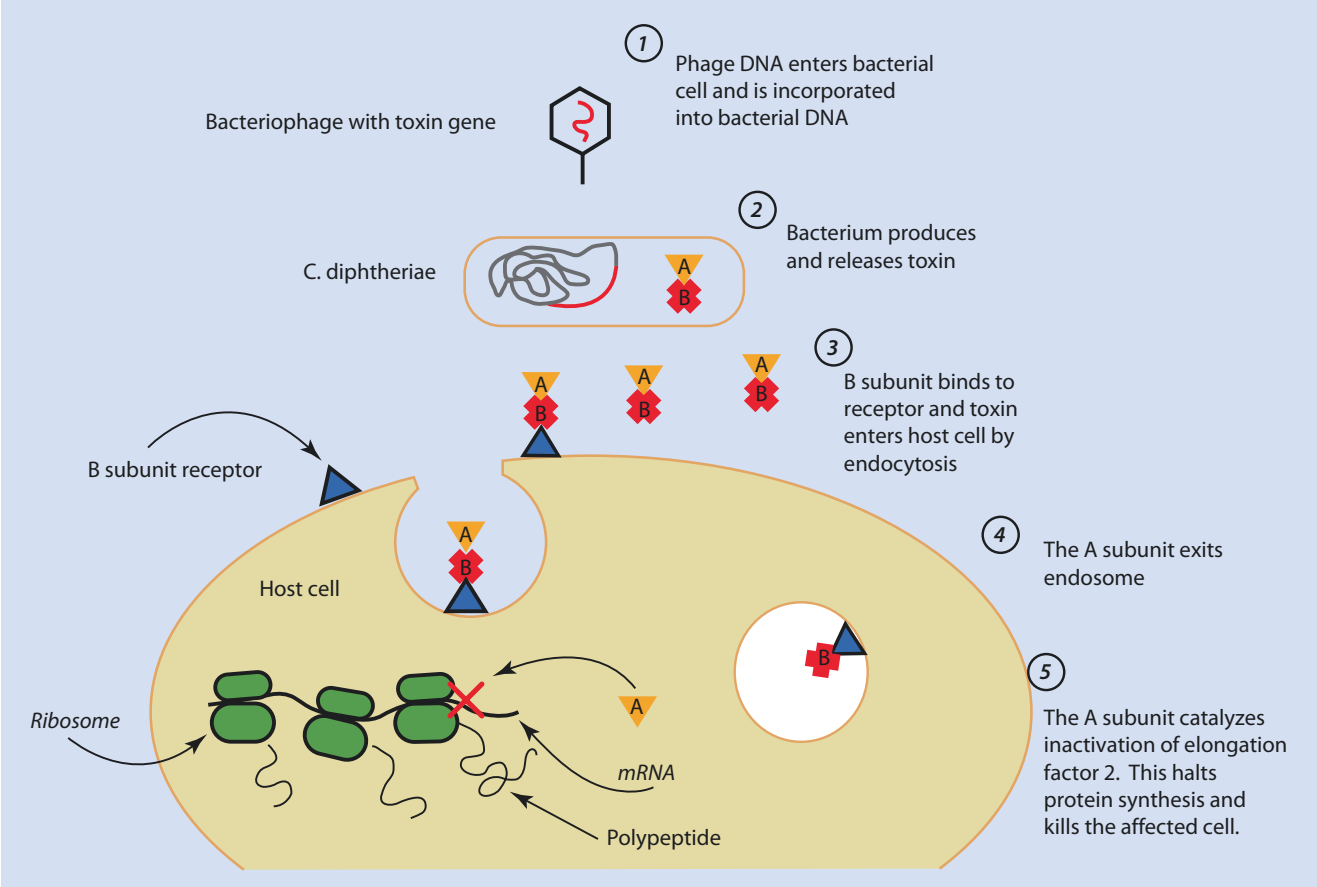



**Fig. 26.9** Stepwise illustration depicting the mechanism of diphtheria toxin. (Courtesy of Mary George PhD, D(ABMM))

respiratory droplets and direct contact with respiratory secretions or cells and fluids from infected skin lesions. Skin infection has caused several recent epidemics in Europe and North America among alcoholics and other disadvantaged groups [20]. Skin carriage can act as a silent reservoir with person-to-person spread from skin sites being more efficient than respiratory sites [21].

The usual incubation period for diphtheria is 2–5 days (may range from 1 to 10 days). Any mucous membrane can get involved like the nasal, pharynx, conjunctivae, and ears. Some patients may present with low-grade fever followed by gradual onset of the characteristic manifestations in 1–2 days. Membranous pharyngitis may present with bloody nasal discharge and in severe forms may progress to extensive cervical lymphadenitis and neck swelling called "bull neck" (Fig. 26.6) [13]. For convenience, we classify diphtheria into different clinical forms based on the location of the disease as listed in ▶ Box 26.5 [14, 22].

The diagnosis of diphtheria is primarily a clinical one although laboratory testing can provide confirmation of toxin production and an isolate for epidemiologic tracking. A swab specimen from beneath the pseudomembrane is the most valuable specimen, but positive results can also be obtained from nasopharyngeal swab samples. Direct examination of swab samples using a Gram stain (Fig. 26.8) has limited utility, but swab samples can be analyzed with

**Box 26.5 Different Clinical Forms of Diphtheria**

- **Respiratory diphtheria**
  - Nasal diphtheria.
  - Laryngeal diphtheria.
  - Pharyngeal and tonsillar diphtheria.
- **Cutaneous diphtheria**
  - Non-healing ulcer.

Neisser or Loeffler methylene blue stains with positive samples demonstrating metachromatic granules. For optimum visualization of these characteristic granules, the bacterium should be grown on Loeffler culture medium before staining [23]. PCR-based direct specimen detection systems for the diphtheria *tox* gene have been described [24]. However, direct detection of *tox* as the sole test has not been recommended since expression of diphtheria toxin must be demonstrated to confirm a diagnosis of diphtheria and because detection of the toxin gene cannot be automatically attributed to a particular species since *C. diphtheriae* as well as *C. ulcerans* and *C. pseudotuberculosis* may also carry this genetic information.

*C. diphtheriae* grows readily on standard microbiology media such as trypticase soy agar with 5% sheep blood, but use of a selective media such as cystine-tellurite blood agar or

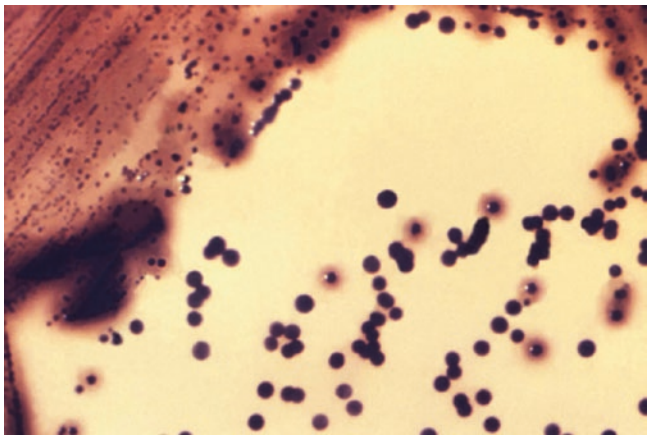


**Fig. 26.10** Shows the characteristic black colonies and brown halo around colonies of *Corynebacterium diphtheriae* on Tinsdale agar. (Courtesy of Centers for Disease Control and Prevention/Dr. Theo Hawkins)

Tinsdale medium aids in recovery from specimens containing commensal respiratory bacteria [23]. Tellurite inhibits the growth of normal respiratory flora, and tellurite reduction leads to the formation of black colonies if the bacterium growing on the medium is able to reduce this compound. The optimum selective culture medium is Tinsdale medium since it allows for the demonstration of both tellurite reductase activity (black colonies) and cystinase activity (brown halo around colonies) both characteristics of *C. diphtheriae*. Figure 26.10 shows the characteristic black colonies and brown halo around colonies of *C diphtheria*. Once bacterial growth is available, identification can be made by manual or automated biochemical methods, chromatographic cell wall analysis, MALDI-TOF mass spectrometry, or molecular genetics-based identification techniques. Once identified, the species can be divided into four biotypes: *gravis*, *mitis*, *belfanti*, and *intermedius* based on differences in colony morphology and biochemical reactions. This method of biotyping has been used for epidemiological tracking of diphtheria cases; however, molecular techniques have proven to be more sensitive in differentiating strains for this purpose.

To confirm toxin production from cultured bacteria, colonies are most often tested using the Elek immunodiffusion method (modified as described by Engler) [25]. PCR-based methods for the detection of the diphtheria toxin gene from cultured bacteria have been developed and validated [26]. However, because a strain can be *tox* gene positive but not be producing toxin, a confirmatory Elek test is necessary to demonstrate the presence of toxin. Although nontoxigenic strains of *C. diphtheriae* (those that do not express toxin in the Elek test or lack detectable *tox* gene by PCR) do not cause diphtheria, they can cause serious disease as has been reported with outbreaks of skin disease, endocarditis, and mortality among homeless people, alcoholics, and IV drug abusers [27].

The Centers for Disease Control and Prevention provides a "checklist for assessing a patient with suspected diphtheria" available at ▶ https://www.cdc.gov/diphtheria/clinicians.html under clinician resources [22]. The checklist allows clinical providers to run the list of symptoms found in the patient if diphtheria is suspected, a probable case, or a laboratory confirmed patients that includes information regarding travel to endemic areas, exposure to a confirmed case of diphtheria, recent exposure with dairy or farm animals, and immunization status. ▶ Box 26.6 lists the different symptoms seen in patients with suspected and probable case of diphtheria.

**Box 26.6 Clinical Presentations in Patients with Suspected and Probable Case of Diphtheria**

- **Suspected case of diphtheria**
  - Nasopharyngitis, pharyngitis, laryngitis, tonsillitis, tracheitis (or any combination of these symptoms), absent, or low-grade fever.
- **Probable case of diphtheria** (suspected case and 1 or more of the following)
  - Bull neck (cervical edema).
  - Myocarditis.
  - Stridor.
  - Subcutaneous or submucosal petechiae.
  - Toxic circulatory collapse.
  - Death.

**Box 26.7 Life-Threatening Complications Associated with Respiratory Diphtheria**

- Cranial and peripheral neuropathies
- Myocarditis with associated heart block
- Renal Insufficiency
- Toxic circulatory collapse
- Upper airway obstruction due to extensive membrane formation or cervical edema (bull neck)

Respiratory diphtheria may progress to severe and life-threatening complications as listed in ▶ Box 26.7. Some patients with pharyngeal diphtheria may have nasal speech due to palatal palsy [14, 22].

There are other disease processes that may be associated with membranous pharyngitis and ▶ Box 26.8 lists the differential diagnosis.

Antitoxin and antimicrobial regimen remains the cornerstone in the care and management of patients with provisional clinical diagnosis of diphtheria [22]. Patients may deteriorate fast, and a single dose of equine antitoxin should be given even before laboratory confirmation becomes available. Clinical indication for antitoxin is available through the CDC – Emergency Operations Center (770 488 7100, ▶ www.cdc.gov/diphtheria/dat.html). The scratch test should be performed to test hypersensitivity to horse serum (which is about 5–20% with allergic reactions) before giving intravenous antitoxin. The intravenous antitoxin is the preferred route to neutralize diphtheria toxin as rapidly as possible (▶ Box 26.9). Antimicrobial therapy is needed not only to stop toxin production but also to eradicate *C. diphtheria* as well as to prevent transmission (▶ Box 26.10) [14, 22].

Diphtheria is usually not contagious 2 days after starting antimicrobial treatment [22]. However, droplet precautions are recommended for patients with pharyngeal diphtheria until two consecutive negative cultures after

**Box 26.8 Differential Diagnoses for Membranous Pharyngitis**

- **Other microbiologic agents**
  - *Arcanobacterium hemolyticum.*
  - *Borrelia vincentii* associated with Vincent's angina (necrotizing gingivitis).
  - *Candida albicans.*
  - *Haemophilus influenzae associated with epiglottitis.*
  - *Staphylococcus aureus.*
  - *Streptococcus pyogenes* (Group A Streptococcus).
  - *Toxoplasma* spp.
  - Viruses (adenovirus, infectious mononucleosis due to EBV, herpes simplex virus).
- **Use of medications**
  - Antineoplastic agents like methotrexate that may cause formation of pharyngeal membrane.
  - Long-term use of corticosteroid (e.g. prednisolone) may cause oral thrush.

**Box 26.9 Suggested Dose Regimen of Antitoxin for Diphtheria Based on Severity of Disease and Duration of Illness**

- **Pharyngeal or laryngeal disease, ≤2 days duration**
  - 20,000–40,000 U antitoxin
- **Nasopharyngeal disease**
  - 40,000–60,000 U antitoxin
- **Extensive disease, ≥3 days duration or diffuse neck swelling**
  - 80,000–120,000 U antitoxin

**Box 26.10 Antimicrobial Therapy of Patients with Clinical Diagnosis of Diphtheria**

| | |
|---|---|
| **Drug of choice:** | erythromycin PO or parenteral, 14 days |
| **Acceptable agents:** | aqueous penicillin G IV, 14 days<br>or penicillin G procaine IM, 14 days<br>or Penicillin V PO |

therapy from both the nose and throat are documented. Contact precautions are recommended for those with cutaneous diphtheria until two negative skin cultures after therapy are documented [14].

The Centers for Disease Control and Prevention provides information regarding close contacts of patients with clinical diagnosis of diphtheria. Close contacts are the household members, and those with direct contact with the case-patient as well as medical staff exposed to the patient's oral or respiratory secretions [22]. The CDC also provides an algorithm in identifying close contacts of case-patient that is available online at ► https://www.cdc.gov/diphtheria/clinicians.html under clinician resources.

The only effective control measure against diphtheria is through universal immunization with a diphtheria toxoid-containing vaccine [14]. Household and close contacts should receive diphtheria toxoid booster appropriate for age. They should receive a 7–10-day regimen of erythromycin (40 mg/kg/day for children and 1 gram/day for adults). If compliance is a concern, a dose of benzathine penicillin may be given (600,000 units for <6 years old; 1,200,000 units for ≥6 years old) to contacts. Household and close contacts should be monitored closely and antitoxin given at the first sign of illness [22].

**Case Study**

**Practical Example**

A 5-year-old girl recently immigrated to the USA a month ago who presented with low-grade fever, bloody nasal discharge, and extensive neck swelling. The young child's immunization record is not available. She is difficult to understand because of language barrier; however, she seems to be having difficulty breathing and clenching her chest for pain. You made the clinical diagnosis of diphtheria, place the patient on droplet precaution, and obtain swab specimen from the adherent membrane on the girl's nasopharynx for culture. You plan on immediately giving antitoxin (► Box 26.9) after the scratch test to neutralize toxin and start antimicrobial therapy with erythromycin (► Box 26.10).

## 26.2.4 Exercises

Please refer to the supplementary information section for answers to these exercises.

1. Describe the pseudomembrane and the "bull neck" signs associated with the clinical presentation of diphtheria.
2. Identify the different end organs affected by the diphtheria toxin.
3. Correspond with the Microbiology laboratory regarding which appropriate specimens to collect from patients with a clinical diagnosis of diphtheria.
4. Describe the different clinical forms of diphtheria and list the differential diagnosis of diphtheria.
5. Discuss the cornerstone of management and complications of patients with the clinical diagnosis of diphtheria.

## 26.2.5 Summary

The universal use of diphtheria-toxoid-containing vaccines has made diphtheria a rare occurrence in the USA. However, diphtheria remains in the differential diagnosis of those presenting with low-grade fever, bloody nasal discharge, adherent membrane in the throat, and extensive neck swelling particularly those with history of travel from endemic areas around the world. It remains a clinical diagnosis, and appropriate antitoxin as well as antimicrobial therapy should be given as soon as possible even before laboratory result confirmation becomes available. Placing the patient with

**Fig. 26.11** Jars of peppers contaminated with *C. botulinum* toxins in a botulism outbreak in Michigan (April 1977). (Courtesy of Centers for Disease Control and Prevention/ Dr. Chas Hatheway)

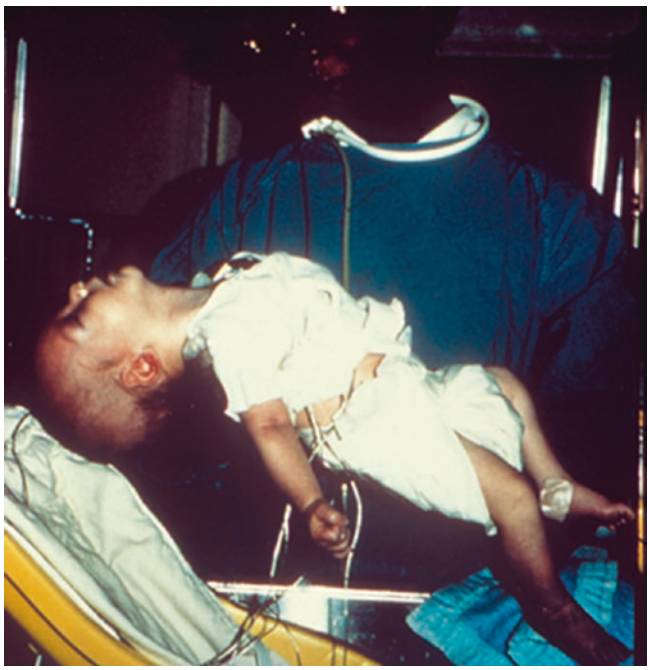


**Fig. 26.12** Infant botulism with characteristic loss of muscle tone noted over the head and neck region. (Courtesy of Centers for Disease Control and Prevention)

diphtheria on appropriate isolation precaution is of utmost importance as well as identifying close contacts of the case-patient which would be helpful in preventing further transmission.

## 26.3 Botulism

### 26.3.1 Introduction to the Problem

There are several forms of naturally occurring human botulism which includes foodborne (Fig. 26.11) [28], infant (Fig. 26.12) [28], wound (Fig. 26.13) [28], and adult intestinal colonization. Botulism is a neuroparalytic disease presenting as acute, without fever, symmetric, descending, flaccid paralysis. There are case reports of iatrogenic botulism

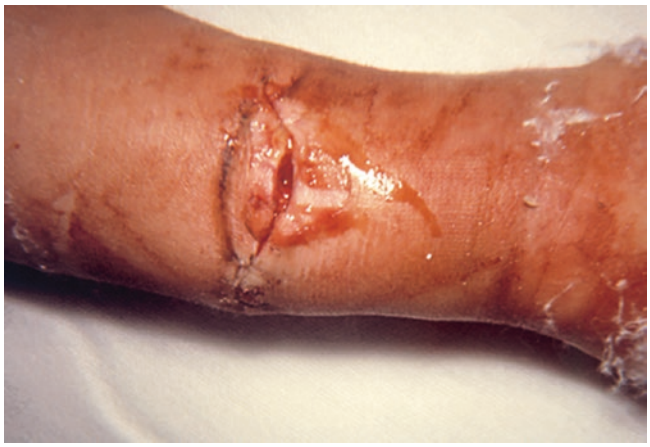


**Fig. 26.13** Wound botulism associated with compound fracture of the right arm. (Courtesy of Centers for Disease Control and Prevention)

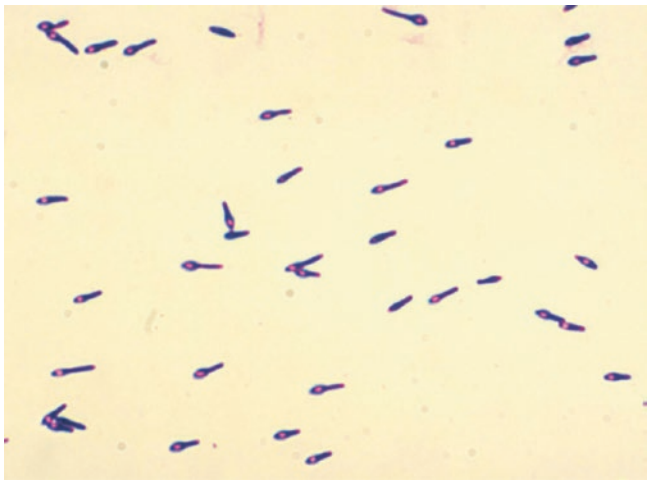


**Fig. 26.14** A photomicrograph of *Clostridium botulinum* with large Gram-positive rod that forms subterminal spores after a Gram stain technique. (Courtesy of Centers for Disease Control and Prevention/ Dr. George Lombard)

associated with administration of excessive therapeutic botulinum toxin in which cranial nerve palsies are followed by symmetric descending, flaccid paralysis [29, 30].

### 26.3.2 Definitions

**Cranial nerve palsies** - associated with botulism presents with diplopia (double vision), dysarthria (slurred or slow speech), dysphagia (difficulty swallowing), and dysphonia (hoarse voice).

### 26.3.3 Basic Concepts

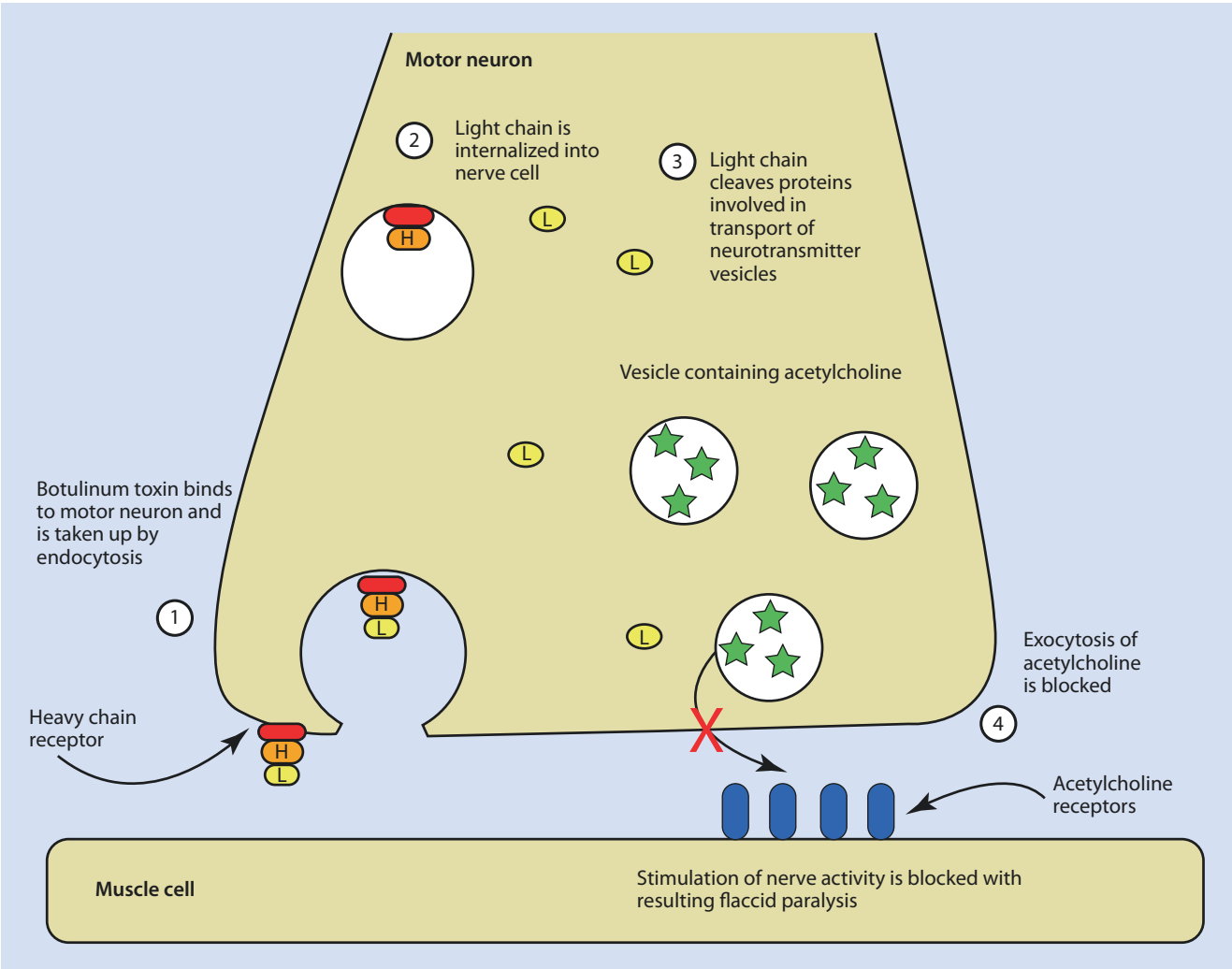
*Clostridium botulinum*, the causative agent of botulism, is a strictly anaerobic, large Gram-positive rod that forms subterminal spores (Fig. 26.14) [28]. The spores of *C. botulinum* are widely distributed in the soil and aquatic environments and can tolerate 100 °C in a pressure canner for several hours [31].

This bacterium produces botulinum neurotoxin, the most lethal poison known [32]. In contrast to the spores, the toxin is readily destroyed by heat. There are seven antigenic serotypes of botulinum toxin (A through G) which serve as useful clinical and epidemiological markers [33] (▶ Box 26.11). For certain serotypes the genes that code for toxin production are associated with unstable genetic elements which can allow for transfer to nontoxigenic *Clostridium* species [34].

**Box 26.11 Antigenic Serotypes of Botulinum Toxin** [29, 33, 46, 51, 52]

- **Toxin serotypes A, B, and E**
  - Main causes of botulism in humans; most cases of infant botulism are due to types A and B.
- **Toxin serotypes C and D**
  - Exclusively found causing botulism in animals.
- **Toxin serotypes E and F**
  - From *C. butyricum* and *C. baratii*; implicated in a few cases of infant botulism.
- **Toxin serotype G**
  - From *C. argentinense*; not associated with disease.

Botulinum toxin is synthesized as a single polypeptide chain of low potency. The toxin is then nicked by a bacterial protease to produce a heavy and a light chain which remain connected. The toxin enters the bloodstream at a peripheral site (e.g., stomach, wound) and travels to the neuromuscular junctions of motor neurons where the heavy chain binds irreversibly to the presynaptic membrane receptors. The toxin enters the cell by receptor-mediated endocytosis with the light chain being internalized into the nerve cell through a protein channel [35]. Once inside the cell, the light chain specifically cleaves a group of neuronal cell proteins (SNARE complex) that are involved in the transport of neurotransmitter vesicles. Because of this action, exocytosis of the neurotransmitter acetylcholine is prevented at the neuromuscular junction with consequent blockage of stimulation of muscle activity and a resulting flaccid paralysis (■ Fig. 26.15) [9]. The body responds to the blockage between the nerve and the muscle by growing new neurons. These try to bypass the blockage and reconnect the nervous system to the muscle [36]. Once the botulinum toxin has all been removed, any new connections will not be blocked, and the pathway will be functional again.




■ **Fig. 26.15** Stepwise illustration depicting the mechanism of botulinum toxin. (Courtesy of Mary George PhD, D(ABMM))

**Box 26.12 Different Kinds of Botulism**

- **Foodborne botulism**
  - Occurs after eating foods (improperly canned, fermented, or preserved homemade foods) contaminated with botulinum toxin
- **Infant botulism**
  - Occurs if spores of the bacteria get into the infant's intestine, germinate, and produce botulinum toxin
- **Wound botulism**
  - Occurs if spores of the bacteria get into the wound (after traumatic injury, surgery, or intravenous drug use), germinate, and produce botulinum toxin
- **Adult intestinal toxemia**
  - A rare kind of botulism due to spores of the microorganism getting into adult's intestine, germinate, and produce toxin similar to infant botulism. Those with medical conditions involving the digestive tract may be at risk
- **Iatrogenic botulism**
  - Occurs if excessive botulinum toxin is injected for cosmetic reasons (for wrinkles) or medical reasons (for migraine headaches)

There are five kinds of botulism and those are described in ▶ Box 26.12 [29, 30].

In foodborne botulism, toxin is ingested with the food in which it was produced. Although commercially canned foods were commonly the source of toxin in the early 1900s, home-canned vegetables, fruits, and fish products are now the most common sources. In some cultures, such as among Alaskan Natives, preferred food preparation practices involving fish fermentation can lead to botulism [37]. In China, homemade fermented beans are the leading cause [38].

Infant botulism and probably adult botulism of unknown etiology have a different pathogenesis in that these illnesses are acquired through the ingestion of spores rather than preformed toxin. The spores are acquired from environmental sources contaminated with soil [39]. In the past, these infections were attributed to honey ingestion, but other sources have emerged since feeding honey to infants has been discouraged [40, 41].

In cases of wound botulism, spores are introduced into a wound, where they germinate and produce toxin. Almost exclusively associated with injection drug use of "black tar" heroin, wound botulism was first reported in the USA in the 1990s [42]. Rare cases of inhalational botulism have been associated with the intranasal use of contaminated cocaine. Inhalation is also one of the potential routes of a bioterrorist attack with botulinum toxin [43].

Botulinum toxin types A and B are approved by the US Food and Drug Administration (FDA) for cosmetic and therapeutic purposes. Iatrogenic botulism cases are uncommon but have been reported with the therapeutic and unlicensed cosmetic use of botulinum toxin A [44, 45]. Some patients after administration of excessive therapeutic botulinum toxin may present with cranial nerve palsies (diplopia, dysarthria, dysphagia, and dysphonia) followed by symmetric descending, flaccid paralysis [29].

**Box 26.13 Incubation Period Varies with the Kind of Botulism**

- **Foodborne botulism**
  - 12–48 h (range, 6 h–8 days) after ingestion of food contaminated with botulinum toxin
- **Infant botulism**
  - 3–30 days after ingestion of spores
- **Wound botulism**
  - 4–14 days after injury

**Box 26.14 Clinical Presentation of Classic Botulism and Infant Botulism**

- **Classic botulism**
  - Blurred vision
  - Diplopia (double vision)
  - Drooping eyelids
  - Dry mouth
  - Dysarthria (slurred or slow speech)
  - Dysphagia (difficulty swallowing)
  - Dysphonia (hoarse voice)
  - Muscle weakness, if not treated may progress to descending paralysis involving respiratory muscles, arms, and legs,
- **Infant botulism**
  - Appear lethargic
  - Constipated
  - Feed poorly
  - Poor muscle tone
  - With weak cry

Botulism occurs after botulinum toxin is absorbed from a mucous membrane or a wound. It is not transmitted from one person to another. Immunity does not develop after the botulism. The incubation period varies depending on the kind of botulism [29] (▶ Box 26.13).

Botulism is a neuroparalytic disease presenting as acute, without fever, symmetric, descending, flaccid paralysis. Botulism is usually preceded by cranial nerve palsies [29, 30] (▶ Box 26.14).

Most hospital laboratories are not properly equipped to process specimens from patients suspected of having botulism. Before collecting any specimens, the medical care provider should call their state health department's or CDC's emergency 24-hr telephone number (770-488-7100) so that appropriate action can be taken to establish the diagnosis, initiate therapy, and investigate the case. Laboratory confirmation of foodborne botulism is the detection of botulinum toxin in serum, stool, or patient's food or the isolation of *Clostridium botulinum* from stool. This case definition is also used for adult and child non-foodborne cases. For wound botulism, laboratory confirmation entails detection of botulinum toxin in serum or isolation of *Clostridium botulinum* from the wound. Bioassays for botulinum toxin are currently the most important laboratory tests for diagnosis of botulism. Currently the only reliable assay is the mouse bioassay together with neutralization of mouse toxicity with type-specific antitoxins [46].

**Box 26.15 Specimens for Diagnostic Assay from the Different Kinds of Botulism**

- **Foodborne botulism**
  - Toxin neutralization bioassay in mice to detect botulinum toxin from enema fluid, gastric aspirate, serum, stool, or suspect foods
  - Enriched selective media to isolate *C. botulinum* from foods and stool
- **Infant botulism**
  - Detect botulinum toxin or botulinum-producing organisms in enema fluid or stool **(best specimen for diagnosis)**
  - Enema fluid may be useful in those with constipation
  - Toxin from serum
- **Wound botulism**
  - Detect botulinum-producing organisms in the tissue or wound
  - Toxin from serum

**Box 26.16 Summary of Treatment Regimens for Botulisms**

- **Equine-derived heptavalent botulinum toxin (BAT)**
  - Treatment of choice for pediatric and adult botulism
  - Infant botulism associated with botulinum toxin type F
- **Human-derived antitoxin or intravenous human botulism immune globulin (BIG-IV or Baby BIG)**
  - Infant botulism due to *C. botulinum* toxin type A or B
- **Antimicrobial agents**
  - Not given in infant botulism except in cases with clinical indication for a concurrent bacterial infection
  - Avoid aminoglycosides since it can worsen the paralytic effects of botulinum toxin
  - Antimicrobial agents in adult intestinal colonization form of botulism is not well established
- **Meticulous supportive care**
  - Fundamental aspect of any forms of botulism
  - Nutritional and respiratory support

Detection of neurotoxin is usually performed on fecal specimens, serum, suspect foods in foodborne cases, and culture fluid following enrichment by growth of the organism. ELISAs, cell culture systems, and biosensor platforms have also been used to detect botulinum toxin [47–49]. PCR assays for detection of genes specific to toxins A, B, and E have been developed. Potential problems with PCR detection are strains that have the gene but do not produce toxin. Anaerobic cultures of serum, stool, and the implicated food, if available, may assist in making the diagnosis. However, samples rarely yield *C. botulinum* because strict anaerobic conditions are required for growth, and competing fecal flora or nontoxigenic *C. botulinum* strains can make recovery difficult [50].

▶ Box 26.15 summarizes the list of specimens for diagnostic assay in cases of botulism [29].

Botulism is a medical emergency [30], and any patients with clinical suspicion for botulism should be managed urgently with antitoxin [29]. Laboratory confirmation of the diagnosis for botulisms should not preclude administration of antitoxin [29]. Equine botulinum antitoxin may be obtained from the Centers for Disease Control and Prevention (CDC) through the state health department which can significantly prevent worsening of botulism and may shorten its presentation if given early [30]. Equine-derived heptavalent botulinum antitoxin (BAT) is the treatment of choice for pediatric and adult botulism which is available from the CDC. BAT contains antitoxin against all seven botulinum types A–G. BAT stops toxemia and ends further uptake of botulinum toxin. The CDC Emergency Operations Center may be contacted for botulism consultation and information regarding antitoxin.

Human-derived antitoxin or intravenous human botulism immune globulin (BIG-IV or Baby BIG) is the antitoxin of choice for infant botulism. Baby BIG is licensed for infant botulism due to *C. botulinum* toxin type A or B and is available through the California State Health Department [29, 30] (▶ www.infantbotulism.org; 510-231-7600). Baby BIG has been reported to significantly decrease the number of days of intensive care unit stay as well as total length of hospitalization. Management should be individualized for infant botulism associated with botulinum toxin type F in which BAT has been used previously [29] (▶ Box 26.16).

**Fig. 26.16** Food containers with dent or bulge should not be consumed since they may contain gas or toxins from *C. botulinum*. (Courtesy of Centers for Disease Control and Prevention/Debora Cartagena)

Recovery from botulism takes several weeks to months. Complications include fatigue and shortness of breath for years and even death in 5% of patients. Mortality is associated from consequences of long-term paralysis or with respiratory failure [30].

There is no available vaccine for primary immunization; however, there are certain control measures that needs to be considered [29]. Young children less than 12 months of age should not be given honey which can be contaminated with *C. botulinum* spores. Safe practices for home-canning should be observed like the use of a pressure cooker (~241 °F) to kill *C. botulinum* spores, bringing the internal food temperature to ~85 °F to destroy the botulinum toxin, and food containers with bulge should be discarded since they may contain gas from *C. botulinum* (Fig. 26.16) [28].

**Case Study**

**Practical Example**

A 6-month-old infant is being evaluated at the local urgent care because of the mother's concern for feeding poorly. The family also noted no bowel movement for several days with weak cry and progressively showing poor muscle tone and today appears lethargic and feeds poorly. On further history his mother reported feeding him honey a week ago from a neighbor who has a bee farm. You are suspicious for infant botulism and immediately make sure the infant is clinically stable before transferring him to the nearest medical center. You reviewed the cornerstone of managing young children with a clinical diagnosis of infant botulism (▶ Box 26.16). You called the local Pediatric Infectious Disease specialist as well as the Centers for Disease Control through the local health department to facilitate diagnosis and appropriate management.

## 26.3.4 Exercises

Please refer to the supplementary information section for answers to these exercises.

1. Identify the different risk factors associated with the development of botulism.
2. Differentiate the various symptoms and clinical presentation of classic botulism versus infant botulism.
3. Correspond with the Microbiology laboratory regarding which culture and bioassays are available locally and which appropriate specimens to collect from patients with a clinical suspicion for botulism.
4. Describe the different clinical forms of botulism.
5. Discuss the different treatment regimens in managing patients with botulism as well as the associated complications.

## 26.3.5 Summary

Botulism is a neuroparalytic disease presenting as acute, without fever, symmetric, descending, flaccid paralysis. There are several risk factors associated with the development of botulism: improperly canned, fermented, or preserved homemade foods (foodborne botulism); ingestion of honey (infant botulism); recent traumatic injury, surgery, or intravenous drug use (wound botulism); and excessive administration of botulinum toxin for cosmetic or medical reason (iatrogenic botulism). Botulism is a medical emergency and any patients with clinical suspicion for botulism should be managed urgently with antitoxin. Laboratory confirmation of the diagnosis for botulisms should not preclude administration of antitoxin.

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# Toxic Shock Syndrome

## Fever, Erythroderma, Conjunctivitis, Shock

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Toxic shock syndrome (TSS) was first described in 1978 [1]. The case series report included seven children and adolescents who had presented with fever, rash, conjunctival hyperemia, headache, confusion, vomiting, and diarrhea. All had evidence of acute renal insufficiency, hepatic insufficiency, coagulopathy, and cardiovascular collapse with prolonged shock. One patient died, one developed gangrene of the toes, and all six survivors eventually developed skin desquamation during convalescence. *Staphylococcus aureus* (*S. aureus*) was isolated from nasopharyngeal, vaginal, or tracheal mucous membranes or from sequestered, localized collections of pus from abscesses or pleural empyema. None of the seven patients described in the initial report had documented bacteremia. The isolates of *S. aureus* were shown to produce an exotoxin which caused a positive Nikolsky sign in the newborn mouse. In the years that followed this case series publication, lay media reports focused substantial attention on the association of TSS with the use of high absorbency tampons. During that period of time, Dr. Todd provided important reminders to both the lay public and to medical personnel that risks were not isolated to the use of tampons speaking of "the myths, partial truths, and gross misconceptions promulgated in the media." Despite the hyperbolic approach used at the time, public media reports ultimately served an important public health education role alerting females to the potential risk for TSS associated with tampon use.

TSS syndrome was subsequently identified as a staphylococcal toxin-mediated disease [2]. The term "superantigen" was coined to describe a stimulus that provokes a substantial expansion and proliferation of T lymphocytes associated with uncontrolled pro-inflammatory cytokine production and release. The ensuing, persistent cytokine storm leads to prolonged and severe shock. Tumor necrosis factor (TNF)-α and interleukin (IL)-1, IL-2, and IL-6 are among the most potent of these pro-inflammatory mediators [3].

The signs and symptoms of TSS are mediated by complex interactions between superantigens expressed by some bacteria and the host's response to their presence. These interactions lead to extensive, uncontrolled immune dysregulation. The pro-inflammatory state results in prolonged shock leading to multi-organ dysfunction. Even with the best available intensive care support, mortality from TSS remains substantial.

Infections caused by strains of bacteria that produce superantigens cause TSS. Superantigens produced by some strains of *S. aureus* include toxic shock syndrome toxin-1 (TSST-1) and staphylococcal enterotoxins B (SEB) and C (SEC). Similarly, some strains of *Streptococcus pyogenes* (*S. pyogenes* or group A beta-hemolytic streptococcus) produce the superantigen streptococcal pyrogenic exotoxin A (SPE-A) [► Call Out Box 27.1].

TSS is an acute systemic illness, characterized by fever, hypotension, and involvement of at least two or more organ systems. Separate case definitions have been established for staphylococcal (► Call Out Box 27.2) and streptococcal TSS (► Call Out Box 27.3).

**Call Out Box 27.1**

Toxic shock syndrome toxin-1, staphylococcal enterotoxins B and C, and streptococcal pyrogenic exotoxin A are superantigens. When expressed and released by bacteria during infection, these toxins stimulate unchecked expansion and proliferation of host T lymphocytes. The ensuing cytokine storm causes toxic shock syndrome.

**Call Out Box 27.2 Case Definition for Toxic Shock Syndrome (Other Than Streptococcal)**

**Clinical Criteria**

An illness with the following clinical manifestations:

- Fever: temperature greater than or equal to 102.0 °F (38.9 °C)
- Rash: diffuse macular erythroderma
- Desquamation: 1–2 weeks after onset of rash
- Hypotension: systolic blood pressure less than or equal to 90 mm Hg for adults or less than fifth percentile by age for children aged less than 16 years
- Multisystem involvement (three or more of the following organ systems):
  - Gastrointestinal: vomiting or diarrhea at onset of illness
  - Muscular: severe myalgia or creatine phosphokinase level at least twice the upper limit of normal
  - Mucous membrane: vaginal, oropharyngeal, or conjunctival hyperemia
  - Renal: blood urea nitrogen or creatinine at least twice the upper limit of normal for laboratory or urinary sediment with pyuria (greater than or equal to 5 leukocytes per high-power field) in the absence of urinary tract infection
  - Hepatic: total bilirubin, alanine aminotransferase enzyme, or aspartate aminotransferase enzyme levels at least twice the upper limit of normal for laboratory
  - Hematologic: platelets less than 100,000/$mm^3$
  - Central nervous system: disorientation or alterations in consciousness without focal neurologic signs when fever and hypotension are absent

**Laboratory Criteria**

Negative results on the following tests, if obtained:

- Blood or cerebrospinal fluid cultures. Blood culture may be positive for *Staphylococcus aureus*.
- Negative serologies for Rocky Mountain spotted fever, leptospirosis, or measles.

**Case Classification**

*Probable*

A case which meets the laboratory criteria and in which four of the five clinical criteria described above are present

*Confirmed*

A case which meets the laboratory criteria and in which all five of the clinical criteria described above are present, including desquamation, unless the patient dies before desquamation occurs

## 27.1 Pathogenesis

Superantigens (SAgs) are major secreted virulence factors of *S. aureus*. Almost every *S. aureus* strain encodes for and can variably produce superantigens when the opportunity arises.

**Call Out Box 27.3 Streptococcal Toxic Shock Syndrome: Clinical Case Definition**[a]

- Isolation of group A streptococcus *(Streptococcus pyogenes)*
  - From a normally sterile site (e.g., blood, cerebrospinal fluid, peritoneal fluid, or tissue biopsy specimen)
  - From a nonsterile site (e.g., throat, sputum, vagina, open surgical wound, or superficial skin lesion)
- Clinical signs of severity
  - Hypotension: systolic pressure 90 mm Hg or less in adults or lower than the fifth percentile for age in children

  *AND*
- Two or more of the following signs:
  - Renal impairment: creatinine concentration 177 µmol/L (2 mg/dL) or greater for adults or at least two times the upper limit of normal for age[b]
  - Coagulopathy: platelet count 100,000/mm$^3$ or less or disseminated intravascular coagulation
  - Hepatic involvement: elevated alanine transaminase, aspartate transaminase, or total bilirubin concentrations at least two times the upper limit of normal for age
  - Adult respiratory distress syndrome
  - A generalized erythematous macular rash that may desquamate
  - Soft tissue necrosis, including necrotizing fasciitis or myositis, or gangrene

[a]An illness fulfilling criteria IA and IIA and IIB can be defined as a *definite* case. An illness fulfilling criteria IB and IIA and IIB can be defined as a *probable* case if no other cause for the illness is identified

[b]In patients with preexisting renal or hepatic disease, concentrations ≥twofold elevation over patient's baseline

Prevailing clones of community-associated methicillin-resistant *S aureus* such as USA300 rarely produce TSS toxin.

The classic SAg expressed by some strains of *S. pyogenes* is SPE-A; however SPE-C and several other novel streptococcal toxins have also been identified that might also be involved in triggering streptococcal TSS. Streptococcal mitogenic exotoxin Z (SMEZ), SPE-G, SPE-H, SPE-I, and SPE-J all possess typical SAg features. Known streptococcal Sag genes, with the exception of SMEZ, SPE-G, and SPE-J, are found on mobile DNA elements.

Traditional antigens must be bound to and presented by MHC molecules before being recognized by a unique T-cell receptor (TcR). In contrast, SAgs bind directly to a conserved locus on the TcR. Bypassing the hypervariable region of the TcR allows the SAg to activate a polyclonal population of T lymphocytes independent of their intended specificity. In some cases, as many as 20% of T lymphocytes are activated by the presence of a single bacterial SAg. The result is widespread activation of T lymphocytes, and other effector cells create the cytokine storm that is responsible for the clinical symptoms seen in patients with TSS [3].

Host defense against SAg-associated diseases relies on the host's ability to neutralize SAgs. Most individuals are exposed to SAgs early in life, so they develop neutralizing antibodies to these proteins by early adulthood. Serum concentrations of anti-TSST-1 antibody, for example, plateaus by age 40 years. For unknown reasons, 20% of people in the USA never develop antibodies to SAg. Children are more likely than adults to lack preformed protective antibodies against the causative toxins explaining why TSS is most common in this age group [4]. Laboratory experiments have shown that high concentrations of interferon-$\gamma$ lead to the suppression of B-cell function – an in vitro observation that may help to explain why anti-SAg neutralizing antibodies fail to develop in response to severe illness [5]. Among otherwise healthy individuals, the risk of developing streptococcal TSS is higher among those with low levels of specific antibodies against the infecting bacterial strain and the SAgs it produces.

Another pathway that contributes to the severe manifestations of streptococcal TSS involves the bacterial M protein, a constituent of the streptococcal cell wall. M protein that is released from the bacterial surface can form aggregates in the blood and tissues because of its ability to bind to fibrinogen, a constituent of blood plasma [6]. The activation of circulating neutrophils by M protein–fibrinogen aggregates leads to endothelial cell damage, thereby triggering intravascular coagulation. The concomitant loss of integrity of the endothelial lining contributes to vascular leakage [7].

Substantial controversy exists regarding the potential association between using nonsteroidal anti-inflammatory drugs (NSAIDs) and the development of group A streptococcal TSS. Hypothetically, a predisposition to TSS could be mediated by the use of NSAIDs secondary to their inhibition of neutrophil function and suppression of fever, thus masking presenting symptoms. Any delay in diagnosis and treatment would be associated with an augmentation of cytokine release. NSAIDs have been shown to suppress granulocyte chemotaxis, phagocytosis, oxidative burst, and bactericidal activity. One prospective study, limited to the pediatric population, demonstrated a statistically significant but low associated risk (odds ratio 1:2) between NSAID use and subsequent development of non-necrotizing invasive group A streptococcal infection. A subgroup analysis from the same study suggested that the slight increased risk applied only to children who were receiving both ibuprofen and acetaminophen [8].

## 27.2 Clinical Manifestations

All of the major clinical manifestations of staphylococcal TSS are listed in ▶ Call Out Box 27.2. The illness is characterized by the abrupt onset of fever and hypotension with evidence of multisystem organ involvement. Profuse watery diarrhea, with or without vomiting, is typical. A generalized macular erythroderma and impressive conjunctival hyperemia give the patient's skin and mucous membranes an "inflamed" appearance.

Approximately 50% of reported cases of staphylococcal TSS occur in menstruating females using tampons, while non-menstrual cases account for the rest. Non-menstrual

cases are described following childbirth or abortion, after surgical procedures, and in association with cutaneous lesions such as burns, cellulitis, or even simple skin abrasions in any age group. Given the dramatic clinical presentation of TSS, it is tempting to assume that a focus of infection will be easy to identify, but an obvious staphylococcal infection may not be appreciated. When an infection is identified, it is typically quite unimpressive. Some examples include small cuts or scrapes, ingrown toenails, recent skin piercings, tattoo sites, and sinusitis [9].

Menstrual cases of TSS are almost universally associated with vaginal colonization by a TSST-1 expressing, toxigenic strain of *S. aureus*. Circumstances that promote bacterial overgrowth and/or cause microscopic abrasions in the vaginal mucosa, such as barrier contraception or tampon use, allow sufficient concentrations TSST-1 to gain access to the bloodstream. In contrast only half of non-menstrual TSS cases are caused by TSST-1. The other half are associated with strains of *S. aureus* that produce staphylococcal enterotoxins, such as SEB and SEC.

Streptococcal TSS (▶ Call Out Box 27.3) usually develops as a result of local soft tissue infection at the site of minor blunt trauma such as a bruise or muscle strain. The local infection at the site of the trauma advances very quickly, progressing to life- and limb-threatening necrotizing fasciitis (NF) and/or myonecrosis within a day or so. Streptococcal NF is associated with a 30–70% mortality rate. The impressive speed with which the infection progresses is responsible for its ugly nickname, "flesh-eating strep."

Varicella infection is a known major risk factor for the development of invasive group A streptococcal infection and streptococcal TSS in children [10–13]. One of the underappreciated benefits of universal immunization against varicella was an associated major decline in reported cases of pediatric group A streptococcal NF. Serious invasive disease including group A streptococcal bacteremia, pneumonia, empyema, osteomyelitis, septic arthritis, and endocarditis can also lead to the development of TSS [14]. Of all cases of invasive group A streptococcal infections in children, fewer than 10% are associated with the development of TSS.

Some cases of streptococcal TSS occur without an identifiable focus of infection, similar to what is seen with the majority of staphylococcal TSS. Accidental or incidental inoculation of *S. pyogenes* into the bloodstream during childbirth, surgical procedures, penetrating trauma, or intravenous drug can be sufficient to lead to TSS.

## 27.3 Epidemiology

Several general differences are noted between TSS caused by *S. aureus* and *S. pyogenes*. Bacteremia and complications that result in tissue necrosis and gangrene are far more common with streptococcal TSS (~50%), while generalized erythema is less common compared to staphylococcal TSS. In streptococcal TSS, *S. pyogenes* is usually isolated from sterile sites. The same is not true for staphylococcal TSS. Culture results from focal sources of infection can be seen with either form of TSS, but securing a microbiologic isolate has always been more challenging with staphylococcal TSS. As such, the case definition for staphylococcal TSS relies more heavily on the constellation of clinical features seen with the disease process than on culture results.

The incidence of streptococcal TSS is highest among young children and the elderly. Mortality rates are much higher in adults (30–80%) than in children (< 5%) reported with staphylococcal TSS [10, 14–17]. Streptococcal and staphylococcal TSS occur with similar frequency among children. Those with streptococcal TSS are younger than those with staphylococcal TSS (3.8 vs 9.5 years; $p < 0.003$).

## 27.4 Differential Diagnosis

The rash seen in TSS is a diffuse macular erythroderma, a dermopathy that resembles a sunburn [▶ Call Out Box 27.4].

Skin desquamation, usually of the hands and feet, typically occurs 1–3 weeks later. It's important to mention this to the patient because the peeling, while harmless, can be quite impressive. The broader differential diagnosis for TSS includes other systemic inflammatory and infectious illnesses that are associated with fever, rash, conjunctivitis, and evidence of end-organ injury. Infectious causes to consider include Rocky Mountain spotted fever, leptospirosis, meningococcemia, measles, and milder forms of exotoxin-mediated staphylococcal or streptococcal infection. Noninfectious inflammatory illnesses that should be considered include acute rheumatic fever, Kawasaki disease, erythema multiforme major, radiation injury, and heavy metal poisoning.

TSS cases may be missed because the diagnosis relies on the recognition of a constellation of clinical features. Some of the diagnostic features, such as rash and subsequent desquamation, may be subtle and therefore overlooked. Some cases may be deemed "sepsis" without appreciating the role of SAg toxins in the illness. It is important to understand how the established case definitions contribute to an underestimate of its true incidence. The case definitions are designed to have high specificity at the expense of sensitivity. In particular, hypotension is a late clinical sign in children and may not occur with aggressive and effective early fluid management. Impending

**Call Out Box 27.4**
The rash seen with toxic shock syndrome is best described as a diffuse macular erythroderma. The patient appears to have an impressive sunburn from head to toe. Other considerations in the differential diagnosis might include exotoxin-mediated infection without toxic shock, heavy metal poisoning, other forms of radiation exposure and injury, some cases of erythema multiforme, and Kawasaki disease.

shock from significant capillary leak in children is heralded by tachycardia and prolonged capillary refill time well before the onset of hypotension [18].

## 27.5 Treatment

The management approach to TSS caused by *S. aureus* and *S. pyogenes* is similar. Once the airway is deemed patent and breathing assessed as adequate, immediate attention to supporting or restoring adequate circulation is initiated. During aggressive fluid resuscitation and implementation of pharmacologic cardiovascular support with inotropic medications, a whole body survey should be performed in search of an infectious focus. Any identified foreign bodies, such as tampons, nasal packing, or recent surgically implanted medical devices, should be removed immediately. Paronychia or ingrown nails found during examination of the fingers and toes should be addressed without delay. Sites of recent piercings or tattoos should be carefully inspected for drainable collections of pus. If a deep tissue infection is suspected or confirmed based on physical examination findings, immediate and aggressive surgical debridement may be life and limb saving (► Call Out Box 27.5). Drainage and irrigation of accessible sites of purulent infection should be performed as soon as possible. Early, aggressive, and repeat surgical debridement is essential for the treatment of necrotizing fasciitis. Limb amputation may be necessary to preserve life.

Because TSS caused by *S. aureus* and *S. pyogenes* are impossible to distinguish from one another clinically, and the disease process if life-threatening, the initial empiric antimicrobial regimen must include coverage for both. Under these circumstances, a combination of *three* antimicrobial agents is recommended, *oxacillin (or nafcillin), vancomycin, and clindamycin*:

1. *Oxacillin* or *nafcillin* is bactericidal for all *S. pyogenes* isolates and all methicillin-susceptible *S. aureus* isolates. These modified penicillins are stable in the presence of the ubiquitous *S. aureus* β-lactamase, have a wide therapeutic window, and are the most potent anti-staphylococcal antibiotics available for the treatment of methicillin-susceptible isolates. Neither agent is active against methicillin-resistant *S. aureus*.
2. *Vancomycin* is bactericidal for all *S. pyogenes* isolates and virtually all *S. aureus* isolates, including methicillin-resistant strains. It has a narrow therapeutic window, requiring careful monitoring of serum concentrations to optimize its antibacterial activity and to avoid toxicity. Regular therapeutic drug monitoring of vancomycin is especially important in critically ill patients where renal function can change quickly and volumes of distribution are difficult to predict. Its use here is specifically to include coverage against methicillin-resistant *S. aureus* isolates. For the treatment of methicillin-susceptible isolates, vancomycin is inferior to oxacillin, nafcillin, and first-generation cephalosporins (e.g., cefazolin). We use vancomycin when we need it for empiric coverage or definitive treatment of methicillin-resistant *S. aureus* infection, but for susceptible isolates, many other agents simply work better.
3. *Clindamycin* is a bacteriostatic protein synthesis inhibitor. It is added initially in an effort to interrupt the translation of any further bacterial exotoxin. Most *S. pyogenes* and many *S. aureus* isolates are susceptible to clindamycin.

All three antibiotics should be given intravenously, at maximum dosages and at appropriate intervals based on age, weight, and/or renal function. Intravenous antibiotic therapy should be continued at least until the patient is afebrile and hemodynamically stable and has negative blood culture results. Total duration of therapy is dictated by the underlying focal infection, if one is identified, and by the patient's clinical response to treatment over time.

Whenever a causative organism is identified in the microbiology laboratory, and the antimicrobial susceptibilities have been confirmed, the empiric antibiotic regimen should be reassessed to determine whether de-escalation is appropriate either by eliminating some of the agents used initially or by replacing one of more agents with more narrow-spectrum options.

Immune globulin intravenous (IgIV) is an adjunctive therapy for TSS with a strong theoretical rationale, with little evidence from clinical trials to support its use routinely [19]. IgIV contains neutralizing antibodies to staphylococcal and streptococcal SAg toxins, has a beneficial effect on opsonization and phagocytosis, and reduces T lymphocyte production of pro-inflammatory cytokines. Taken together, these neutralizing and anti-inflammatory properties seem to be ideal properties of a medication used for the treatment of TSS. A single randomized clinical trial of IgIV vs placebo for the treatment of TSS in adult patients was terminated prematurely because of difficulties in enrollment [20]. Available data from the partially enrolled cohort suggest that

**Call Out Box 27.5 Management of Toxic Shock Syndrome**

Early and aggressive fluid management sufficient to maintain adequate cardiac filling pressures and systemic venous return

Monitoring for and supporting evolving multisystem organ failure including medication dosing modifications as needed based on renal or hepatic dysfunction

Parenteral antimicrobial therapy at maximum doses to include:

1. Oxacillin or nafcillin, bactericidal cell wall inhibitors active against methicillin-susceptible *S. aureus and S. pyogenes*
2. Vancomycin, a bactericidal cell wall inhibitor active against methicillin-resistant *S. aureus and S. pyogenes*
3. Clindamycin, a bacteriostatic protein synthesis inhibitor used to interrupt synthesis of toxin
4. Immune globulin intravenous should be considered for infection refractory to several hours of aggressive therapy or in the presence of an undrainable focus or persistent oliguria with pulmonary edema
5. Surgical consultation as necessary for debridement and/or abscess drainage

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compared to placebo, patients treated with IgIV had reduced mortality, reduced sepsis-related organ failure assessment scores, and more robust SAg neutralization. Results from a 2009 provider survey on TSS management in the pediatric population in the UK indicated that 67% of respondents routinely included clindamycin in the initial empiric antibiotic regimen and 20% used IgIV. Eight pediatric deaths were identified during the survey. None of those who died had been given IgIV [17]. Conversely, an Australian retrospective series of 62 pediatric patients with TSS all survived-clindamycin was included as part of the initial empiric antibiotic regimen in 90% of cases, and adjunctive therapy with IgIV was used in 48% of cases. Approximately half of the patients described in the series had received both clindamycin and IgIV [14]. Results from an active, prospective, statewide surveillance for invasive group A streptococcal infections across Australia suggest that including clindamycin in the treatment regimen of patients with severe infection, including TSS, substantially reduces mortality and that this benefit may be further enhanced with concurrent administration of adjunctive IgIV [21].

The role of adjunctive IgIV therapy in pediatric TSS syndrome remains understudied. While adult data consistently suggest improved survival when IgIV is used, similar data are not likely to emerge for the pediatric population because childhood mortality from TSS is already quite low. Going forward, attempts to measure therapeutic benefits associated with IgIV use for TSS in the pediatric age group should choose outcome measures other than survival [22, 23]. Taken together, existing data appear to support a therapeutic benefit of including IgIV in the treatment of TSS, with the stronger evidence coming from observations in adults. IgIV appears more likely to be beneficial when used early in the course of illness, but the American Academy of Pediatrics Committee on Infectious Disease guidance states that IgIV "may be considered for infection refractory to several hours of aggressive therapy" [24] (▶ Call Out Box 27.5). If used, the optimal dose of IgIV remains unknown [24].

Clindamycin and IVIG are relatively safe treatments, and despite the absence of definitive trials, reasonable evidence and expert opinion support their use as adjunctive therapy for both children and adults with TSS. Given the potential for a significant benefit with limited added risk in a life-threatening disease process, adjunctive therapy with IgIV should probably be given to any patient with suspected or proven TSS. Decisions regarding adjunctive treatment(s) should not detract from the immediate and critical importance of confirming a patent airway, verifying adequate breathing, restoring and supporting circulation, identifying and removing all sources of infection, and starting empiric parental antibiotic therapy.

Household contacts of patients with severe invasive group A streptococcal disease, including TSS, are at somewhat higher risk of developing severe infection compared to the general population. This modest increase in risk is not sufficient to justify routine testing for group A streptococcus pharyngeal colonization. Because of the elevated risk of invasive group A streptococcal disease among certain populations, such as individuals with human immunodeficiency virus infection, varicella, and diabetes mellitus and those who are 65 years and older, providers may choose to offer targeted chemoprophylaxis to some household contacts. Secondary cases of invasive, severe group A streptococcal infections in children are uncommon. Chemoprophylaxis is not currently recommended in schools or child-care facilities in the USA after an index case is identified. Public health recommendations for circumstances that indicate a need for post-exposure chemoprophylaxis of close contacts, based on expert opinion, vary by country [24, 25].

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# Bacteremia and Bacterial Sepsis

## The Patient with A Positive Blood Culture

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**Learning Objectives**

- Differentiate between bacteremia, bacterial sepsis, and septic shock.
- Understand the challenges of identifying a patient with bacteremia based on clinical factors.
- Identify the usual pathogens that cause bacteremia in different age groups.
- Describe the treatment for patients with bacteremia and sepsis.

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## 28.1 Definitions

***Bacteremia*** - The presence of bacteria in bloodstream.

***Systemic inflammatory response syndrome (SIRS)*** - A body-wide inflammatory response defined by two or more of the following criteria – abnormal temperature (>38 °C or <36 °C), abnormal heart rate (tachycardia or bradycardia), tachypnea, and abnormal white blood cell count (leukopenia or leukocytosis).

***Sepsis*** - A life-threatening organ dysfunction caused by dysregulated host response to infection.

***Sepsis-related organ failure assessment (SOFA) score*** - A scoring system used to predict the severity of sepsis and associated mortality based on six criteria (respiratory (PaO2/FiO2 ratio), cardiovascular (mean arterial pressure <70 mmHg or use of vasopressors), hepatic (total bilirubin), renal (creatinine or poor urine output), coagulation (platelet count), and central nervous system (Glasgow Coma Scale)). All criteria are graded from 0 to 4. Higher scores indicate more severe sepsis.

***Septic shock*** - Inadequate oxygen delivery to end organs due to sepsis resulting in metabolic derangements.

## 28.2 Introduction

Humans and bacteria live in symbiosis. Bacteria that inhabit the skin and the mucous membranes of the gastrointestinal, genitourinary, and upper respiratory tracts are referred to as "normal flora." Commensal bacteria are not typically invasive, but injuries to or disruptions in the skin or mucous membranes provide an opportunity for the resident bacteria to bypass the anatomic barrier and cause infection. Bacterial pathogens that are not considered normal flora cause infections by invading healthy or injured barriers using a variety of different virulence factors. The bacteria may invade the bloodstream directly to cause bacteremia. Alternatively, a localized infection may develop at the entry site serving later as a source for intermittent bacteremia. The resulting illness severity depends on the original source of the infection, the specific bacteria involved, the tissues and organs that are infected, and a variety of patient-specific factors.

In many instances, the source of infection that led to the finding of a positive blood culture is obvious, even expected. For example, it would be quite typical to encounter a positive blood culture for *Streptococcus pneumoniae* from patient with lobar pneumonia. Under other circumstances the underlying source for the bacteremia is not immediately obvious and needs to be explored. Clues about an underlying source of infection should first be collected during the medical history. The chief complaint, the presenting signs and symptoms, and the presence of known underlying medical problems can all provide important clues. A discussion that includes details about the patient's past medical history, any known exposures to illness, sexual behaviors, occupation, contact with animals, and travel history can help identify risks for specific infections.

**Call Out Box 28.1**
**The Systemic Inflammatory Response Syndrome "SIRS"**
**Abnormalities in two or more of the following:**
Body temperature: Hypothermia <36 ° C **or** fever >38 ° C
Heart rate: Tachycardia **or** bradycardia
Respiratory rate: Tachypnea
Total white blood cell count: Leukopenia **or** leukocytosis

Clinically, the systemic signs and symptoms of bacteremia and sepsis, such as fever and malaise, overlap with those seen with most infections. The systemic inflammatory response syndrome, or SIRS, is a constellation of features that are defined by specific clinical criteria. To meet the definition for SIRS, a patient must have two or more of the following findings: temperature abnormality (hypothermia <36 °C or fever >38 °C), abnormal heart rate (tachycardia or bradycardia), tachypnea, and abnormal total white blood cell count (leukopenia or leukocytosis) based on age-specific parameters [▶ Call Out Box 28.1]. It is important to acknowledge that SIRS can occur in the presence or absence of a bacterial infection. When an infection is suspected or confirmed as meeting SIRS criteria, the syndrome is known as *sepsis*.

## 28.3 Laboratory Studies in the Evaluation of Possible Bacteremia

The gold standard used to document the presence of bacteremia is the blood culture. Most typically, venous blood samples are obtained, but arterial samples are also acceptable. It is important to remember that proper topical antiseptic cleaning of the skin with iodine, betadine, or chlorhexidine is required before puncturing the skin with a needle. When done properly, growth of skin contaminants in the culture is rare. The blood volume used to inoculate the blood culture bottle is very important. The bottles used for liquid broth blood culture systems are imprinted with labels that clearly identify the minimum and maximum volumes of blood that should be added. The practice of only introducing the minimum recommended volume per bottle as a standard practice is discouraged since the sensitivity of the test correlates directly with the total volume of blood used for the culture as long as the maximum volume is not exceeded. In the case of blood cultures, more, up to the maximum recommended volume, is better. With the exception of newborns, where a blood culture is defined as a single aerobic bottle inoculated with 1–3 ml of blood, the term "a blood culture" refers to a set

that includes one aerobic bottle and one anaerobic bottle. As such, if two blood culture sets are collected, the laboratory will receive a total of four bottles, two aerobic and two anaerobic. Depending on the culture system used, each bottle may allow a maximum of 10 ml of blood, so the act of collecting two sets of blood cultures (four bottles), with the objective to add the maximum amount of blood volume to each, amounts to a 40 ml blood draw if no other laboratory tests are requested. The sensitivity of two blood cultures to detect bacteremia in adults, when the blood volumes are optimized, is greater than 95%. Similar volumes of blood are not appropriate when drawing blood cultures from newborns, infants, and very young children, yet lower-volume cultures have a sensitivity of 98% or better. Their very high bacterial loads explain the explanation for the higher sensitivity of blood cultures obtained from bacteremic young children. Adults with bacteremia typically have one or fewer colony-forming units of bacteria per 10 ml of circulating blood. In contrast, bacteremic infants typically have between one and ten colony-forming units per 1 ml of circulating blood. The presence of between 10- and 100-fold more bacteria per unit volume of blood explains how the occasional neonatal blood culture submitted to the laboratory with a half ml of blood or less can still yield a positive result. The volume-dependent sensitivity of blood cultures should be kept in mind when considering appropriate volumes of blood cultures that need to be collected under special circumstances, such as concerns for bacterial endocarditis. The time to optimize the sensitivity of the cultures being collected is during the initial draw especially if broad-spectrum empiric antibiotic therapy is prescribed after the samples are secured. Another important recommendation to follow when obtaining blood cultures is to collect each culture from a separate sampling site. Collecting two blood cultures (four bottles) requires two separate blood draws. It's perfectly reasonable to expect to be able to draw 40 ml of blood from a single vein, and bacteria are evenly distributed throughout the vasculature, so the specific site used to collect the blood is unimportant. If bacteria are present and a sufficiently large volume blood draw is used to inoculate the bottle, the culture will identify the culprit. The rationale for collecting blood cultures from separate sites is instead recommended to facilitate interpretation of results when one or more of the cultures flag positive for a bacterium that could equally be a skin contaminant or a true cause of bacteremia. When multiple blood cultures are collected from different sites, and only one bottle is reported to be positive for a bacterium known to colonize the skin, it becomes easy to dismiss that one bottle as a contaminant. If a 40 ml blood draw is collected from a single site, and all four bottles are positive for the same bacterium, it's not clear if the result stems from contamination during collection or reflects a true bacteremia. If the patient has already received empiric antibiotic therapy, further testing to clarify the diagnosis will not be helpful. Each blood culture should be collected from different, freshly prepared sites.

After the blood culture bottles are inoculated, they are brought to the clinical microbiology laboratory. There, the bottles are incubated in a laboratory instrument designed to screen each bottle for possible bacterial growth several times each hour. Each bottle contains a matrix plug that sits on the bottom. The biochemistry of the matrix is altered when the pH of the broth medium undergoes subtle fluctuations. If bacteria are present in the broth, as they replicate, they metabolize the nutrients, generate acids, and cause incremental drops in the pH of the liquid broth. As the bottles rotate in the instrument, they pass a laser that hits the matrix in the bottom of the bottle. If the pH of the bottle drops, the laser detects the change in the matrix, and the instrument alarms, indicating to the laboratory technician that one of the blood cultures is suspected to be positive. The technician removes the bottle from the instrument, performs a Gram stain on the broth and subcultures the contents of the bottle onto solid culture media. The Gram stain result is immediately communicated to the care team as a positive blood culture growing Gram-positive or Gram-negative bacteria, with a brief description of the organism's morphology, such as diplococcic, cocci in clusters, pleomorphic rods, or branching rods. Colonies of bacteria typically become visible on the solid media after 24 h of incubation. When sufficient growth of the bacteria allows, the organism is identified, and antimicrobial susceptibility testing performed.

Most positive blood cultures are identified within 48 h of collection, but clinical laboratories typically hold all blood cultures for at least 5 days before finalizing the culture report as negative. Cultures that are first detected to be positive after 72 h of incubation should be viewed with suspicion, especially if the organism is ultimately identified as a bacterium known to colonize the skin. In some circumstances, laboratory personnel identify an unusual organism that is known to grow very slowly. Such cases need to be considered individually in the context of the patient's clinical condition.

Blood cultures take time, but the results provide crucial information that helps to guide patient management. At the time of presentation, several other laboratory studies are typically performed. Results for many of the more standard tests, such as a complete blood count (CBC) with differential, inflammatory biomarkers, urinalysis, and blood lactate, are available within a few hours, and while none are specific for bacterial infection or bacteremia, observed patterns can certainly heighten or reduce one's clinical suspicion. When reviewing results from a CBC with differential, a leukocytosis with a predominance of neutrophils, is suggestive of a bacterial infection, especially if band and other immature forms are present. The presence of leukopenia is more typical of viral infections, but its presence in a severely ill patient is worrisome for neutrophil depletion, a laboratory finding seen in advanced bacterial sepsis.

Inflammatory biomarkers are expected to be elevated during periods of inflammation, including serious bacterial infections. Commonly used laboratory tests include the erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and procalcitonin (PCT). The erythrocyte sedimentation rate (ESR), or "sed rate," is the rate at which red blood cells sediment by gravity over a period of 1 h. The laboratory

result is reported as the millimeters of plasma present above the sedimented erythrocytes in a standard-sized tube after 1 h (mm/h). A high number indicates that the cells fell to the bottom of the tube quickly. This occurs during conditions of acute inflammation because of the presence of inflammatory proteins, especially fibrinogen, that stick to the cells causing them to stack up in rouleaux formation. Individual erythrocytes sediment slowly, while stacked groups of cells sediment quickly, resulting in an elevated ESR. Hepatic synthesis of C-reactive protein (CRP), like fibrinogen, is augmented during periods of systemic inflammation. These and other proteins that are produced in the same pattern are referred to collectively as "acute-phase reactants." Measured serum concentrations of CRP can increase 100-fold or more if the inflammatory stimulus is sufficiently robust. The precise role, if any, of CRP in the innate host defense against bacteria is unknown. Serum procalcitonin concentration is another nonspecific biomarker used to predict the likelihood that a patient's clinical condition is a result of a bacterial infection. Extreme elevations have been shown to be quite specific for bacterial disease, while moderate elevations are more difficult to interpret with a degree of certainty.

When evaluating a patient with possible or proven bloodstream infection, it's important to consider the possibility that an underlying focal infection is present because the quality and/or its anatomic location may require specific changes in management. The pathogen identified in a positive blood culture may also provide necessary clues that point toward a focal infection in a specific anatomic location. For example, blood cultures that are positive for *Escherichia coli* or a *Klebsiella* species are suggestive of a urinary tract source, while blood cultures growing a *Salmonella* species implicate the gastrointestinal tract as the entry site.

Individuals with pyelonephritis usually have flank pain and/or clear-cut urinary symptoms, but not always. Some individuals, particularly young children and elderly adults, present with fever, nausea, vomiting, and abdominal pain, without localizing signs. Laboratory results from a CBC and biomarkers of inflammation would likely support a bacterial cause but, like the symptoms, are nonspecific. The first hint that the urinary tract is the source in such cases comes when the laboratory reports results of a urinalysis. The detection of leukocytes, leukocyte esterase, and bacteria, the most obvious abnormalities that point to a urinary tract infection, is most likely. A urine culture should also be included in the diagnostic evaluation. Paying close attention to the technique used to collect the urine sample to avoid contamination with urogenital flora helps to avoid problems with interpreting the results later. Adults and most children who are toilet trained (with parental help) are able to provide a clean-catch specimen after being provided with careful instructions on how to do so. Urine obtained by catheterization is most appropriate when collecting samples for culture from infants and young children. Urine collected into a pouch or bag should never be sent for culture since the sample will be compromised and any bacteria that grow will not likely reflect conditions of the bladder or the upper urinary tract. Urine cultures that are reported to grow more than one species of bacteria should be viewed with suspicion that the sample was contaminated.

## 28.4 Anatomic Foci of Infection that Are Associated with Bacteremia

Bacteremia that is associated with an intravascular source is, by definition, continuous. Continuous bacteremia occurs with infectious endocarditis, thrombophlebitis, and intravascular catheter-associated infections. Intermittent bacteremia occurs when the source of infection is elsewhere such as the lung or the kidney. Some pathogens have virulence factors that facilitate invasion directly across mucous membranes by evading first-line innate defense measures and/or taking advantage of a more impaired host immune system.

Neonates are especially prone to bacteremia due to their immature immune defenses. Perinatal colonization with virulent bacteria such as *Streptococcus agalactiae* (group B streptococcus), Streptococcus pyogenes (group A streptococcus), *Staphylococcus aureus*, *Escherichia coli*, or *Listeria monocytogenes* can be associated with direct invasion with rapid development of sepsis. Beyond the newborn period, bacteremia associated with *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae* type b was once very common among children under 5 years of age. Routine immunization practices have led to substantial reductions in invasive disease caused by these organisms in recent decades, but not all serotypes of *S. pneumonia* and *N. meningitidis* are represented in vaccines explaining why they still account for a substantial number of blood culture isolates. *S. pneumoniae and S. aureus* remain the most common pathogens to cause bacteremia and sepsis across all age groups.

Several underlying conditions are associated with an increased risk of developing bacteremia. Patients who require the presence of an indwelling central venous catheter for any reason and those who have injury to or disruption of the skin or mucous membranes are at risk for bloodstream infections. Immunosuppressing diseases and their treatments also place patients at risk. Rates of bacteremia are also increased in patients with neutropenia, asplenia, and deficiencies in humoral immunity, properidin, and terminal complement components.

## 28.5 Management of Sepsis

All acutely ill patients, including those with suspected sepsis, require a stepwise initial assessment of their airway, breathing, and circulation ("the ABCs"). Airway patency is always assessed first. Breathing and the general level of respiratory distress are evaluated next, followed by an assessment of circulation. SIRS criteria can be used to identify patients at high risk for having an acute bacterial infection.

**Call Out Box 28.2**
**qSOFA criteria indicate a positive screen if two or more are present:**
- Respiratory rate of more than 22 breaths per minute
- Systolic blood pressure less than 100 mm Hg
- Glasgow Coma Scale less than 15

**Call Out Box 28.3**
**Criteria used for SOFA scoring:**
- PaO2 to FiO2 ratio
- A mean arterial pressure or use of vasopressors
- Total serum bilirubin
- Serum creatinine or low urine output
- Platelet count
- Glasgow Coma Scale

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. The sepsis-related organ failure assessment (SOFA) score is used to predict the severity of sepsis and associated mortality. The quick SOFA (qSOFA) is a screening tool that should be used to assess patients where infectious causes had not previously been considered, or to evaluate sepsis severity in a patient with a known infection. The presence of at least two of three qSOFA criteria indicate a positive screen [► Call Out Box 28.2]. The SOFA score relies on six criteria, each with a severity index ranging between zero and four [► Call Out Box 28.3].

## 28.6 Treatment

Once the ABC's are assessed and necessary resuscitation interventions are in place, empiric antibiotics are administered to sterilize the blood and treat any underlying tissue or organ infection. Surgical intervention may be necessary to drain abscess collections. Respiratory and cardiovascular supports are provided as necessary.

Broad-spectrum empiric antibiotics should be given to all patients with suspected or proven bacteremia. Antibiotic choices depend on the clinical circumstances and on underlying host factors. Examples of broad-spectrum antibiotics that are used in different circumstances included extended-spectrum penicillins (e.g., ampicillin-sulbactam, piperacillin-tazobactam), advanced generation cephalosporins (e.g., ceftriaxone, ceftazidime, cefepime, ceftaroline), carbapenems (e.g. imipenem, meropenem), advanced generation fluoroquinolones (e.g. levofloxacin, moxifloxacin), vancomycin, and linezolid. Once blood culture reveals the microbiologic diagnosis, and antimicrobial susceptibilities are known, antibiotic de-escalation should be considered so that the remaining course of treatment specifically targets the etiology with the most narrow-spectrum and best-tolerated agent(s).

The most severe form of sepsis leads to septic shock, heralded by profound circulatory compromise with metabolic abnormalities. Patients in septic shock have higher mortality when compared to those with sepsis alone. The initial treatment of septic shock includes intravenous fluid resuscitation with isotonic crystalloid fluids. It is important to regularly reassess the patient's blood pressure, perfusion, and respiratory status. Subsequent boluses of fluid can continue up to 60 ml/kg or 3 L. Should this amount of fluid resuscitation fail to stabilize the patient's cardiovascular status, or if pulmonary edema develops, vasopressors such as epinephrine, norepinephrine, phenylephrine, dopamine, or dobutamine are added to help support circulation.

## Further Reading

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# Catheter-Related Bloodstream Infections (CRBSIs)

## Fever in A Patient Who has A Central Venous Catheter in Place

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**Learning Objectives**

- Recognize the clinical presentations of catheter-related bloodstream infections
- List common etiologies of catheter-related bloodstream infections
- Discuss diagnostic methods used to confirm a catheter-related bloodstream infection
- Formulate a treatment plan for a patient with a catheter-related bloodstream infection
- Identify prevention measures that are successful in reducing rates of catheter-related bloodstream infections

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## 29.1 Introduction to the Problem

The use of intravascular devices has become a welcome aspect of caring for patients with medical problems that require regular infusions of medications or blood products and/or frequent blood tests. The increasing need for secure and/or long-term intravascular access has been met by progress in medical device technology [1–3]. As a result, central venous catheters (CVCs) are now widely utilized to address the needs of patients with a broad array of chronic and acute medical problems. CVCs are now routinely placed and used for hemodialysis, cancer chemotherapy, parenteral nutrition, and monitoring and delivery of intravenous treatments necessary during intensive care. However, as with the use of all medical devices, the use of intravascular devices comes with measurable risks. In the United States, the estimated annual numbers of catheter-related bloodstream infections (CRBSIs) are substantial, with the highest rates reported from patients receiving intensive care and those undergoing treatment in outpatient hemodialysis settings [4]. Although the overall incidence of CRBSIs is declining in intensive care units (ICU) settings, a substantial number of infections continue to occur, contributing to healthcare-associated costs, morbidity, and mortality [5, 6].

The variety of intravascular devices used in modern healthcare includes devices inserted into veins or arteries. Venous catheters are used to infuse medications or blood products and, when placed centrally, to continuously monitor central venous blood pressure. Commonly used devices include the ubiquitous, short-term use, peripheral intravenous catheters (peripheral IVs), longer-term use peripherally inserted central catheters or "PICC lines," and central venous catheters that are placed surgically or inserted percutaneously. Arterial catheters, such as those placed percutaneously into the radial artery, are used to directly and continuously monitor systemic blood pressure. Placement also facilitates arterial blood sampling needed for diagnostic testing (e.g., arterial blood gas determinations). Much less frequently, pulmonary artery catheters are placed for diagnostic use in the intensive care setting. By far, the vast majority of CRBSIs are associated with central venous catheters.

## 29.2 Definitions

**Catheter-related bloodstream infection (CRBSI)** – bloodstream infection attributed to an intravascular device [7].

**Central line-associated bloodstream infection (CLABSI)** – bloodstream infection in a patient who had a central line within the 48 h period before the onset of symptoms, not related to an infection at another site. The definition is commonly used for surveillance purposes in an effort to standardize reporting from all accredited US hospital systems [7].

**Short-term CVCs** – venous catheters generally used for temporary access including non-tunneled central catheters that are placed percutaneously. The catheter exits the skin in the vicinity of the venous cannulation site. Peripherally inserted central catheters or "PICC lines" are long devices that are inserted via a peripheral vein and advanced so that the catheter tip sits in a central vein.

**Long-term CVCs** – surgically implanted central venous catheters with a tunneled, subcutaneous portion of the catheter located between the entry site on the skin surface and the site where the catheter enters the central vein. A cuff is typically present just under the skin where the catheter exits to the outside. These devices are used for long-term vascular access to deliver chemotherapy, medications that are needed for extended periods of time, or for hemodialysis. Brand names of several commonly used devices include Hickman®, Broviac®, Groshong®, Leonard®, and Neostar® catheters [8]. It's not unusual for healthcare providers to refer to all long-term CVCs using the single brand name most familiar to them even though different patients have different brand devices. The patients learn the terminology from the providers, so the brand name used by the patient to describe their "line" may not be the brand that they actually have. Each brand, however, is manufactured somewhat differently. Some are made of silicone, while others are made of polyurethane. Some are cuffed, while some are not. Some have valves. Some are available with single, double, or triple lumens. Some are open at the distal end, while others only have side port openings. Under most circumstances, the specific brand is inconsequential. In circumstances where the precise brand does need to be known, it is important to refer back to the procedure notes made during placement rather than relying on the brand "nickname" used. An important example is when a 70% ethanol lock is being considered as a measure to prevent infection. Silicone catheters tolerate the ethanol dwells quite well, but catheters composed of polyurethane have a tendency to soften creating a risk for cracks and leaks.

**Totally implantable venous access device** – these devices are similar to long-term CVCs, but the appliance itself is implanted subcutaneously and does not exit through the skin. The subcutaneous segment of the device contains a small reservoir covered by a diaphragm. The reservoir communicates directly with proximal portion of the catheter. During surgical placement, the catheter is tunneled from the reservoir to the site where it enters the vein. The implanted device is a closed system until access is needed to infuse medication or to collect blood for diagnostic testing. To do so, the subcutaneous reservoir is identified, and a specially designed needle is inserted percutaneously so that it penetrates the diaphragm and enters the reservoir. These implanted long-term vascular devices are associated with low rates of infection [8, 9]. It is helpful to be familiar with the trade name(s) of the commonly used devices in one's healthcare community because patients, nurses, and providers typically avoid referring to them as "totally implantable venous access devices," preferring instead to use the brand name or, even more simply, **the port**. Conveniently, all of the available intravascular devices included in this category have the word "port" in their name. Examples of available brand names included Port-A-Cath®, BardPort®, PassPort®, Medi-port®, and Infusaport®.

## 29.3 Basic Concepts

### 29.3.1 Clinical Presentation

The majority of CRBSI cases present as fever without a source. Other clinical manifestations include catheter malfunction, hemodynamic instability, altered mental status, and other signs of sepsis. Fevers that occur after a catheter is accessed, manipulated, or flushed should raise suspicion for infection. Complications of infected catheters may include suppurative thrombophlebitis, endocarditis, and a host of metastatic infections. The distal ends of central venous catheters most typically sit in the superior vena cava or subclavian vein. The device is intravascular, so when an infection develops, a low-grade, continuous bacteremia or fungemia occurs. Pathogens that are dislodged from the distal portion of the device, often along with fragments of an associated thrombus, travel from the central veins of the chest into the right atrium, across the tricuspid valve into the right ventricle, continuing across the pulmonic valve to the pulmonary artery out to the lungs, settling in the pulmonary microvasculature. Endocarditis of the right side of the heart develops when there has been seeding of the tricuspid or, less commonly, the pulmonic valve. Septic pulmonary emboli are associated with varying degrees of shortness of breath, cough, and tachypnea. In some cases, pathogens make their way across the pulmonary microvasculature into the pulmonary veins, to the left atrium, across the mitral valve to the left ventricle, and past the aortic valve to the aorta into the systemic circulation. Septic emboli to the skin may present as petechial, papular, nodular, or pustular rashes, skin abscesses, or ecthyma gangrenosum. Hematogenous seeding of the bone is associated with localizing pain, erythema, and swelling. Infected emboli to the liver, spleen, or kidney may be associated with abdominal pain, nausea, or vomiting, especially as abscesses are formed. Headache, vomiting, and focal neurological symptoms are typical for embolic stroke [10–13].

Routine screening for the presence of these complications beyond a chest radiograph is not typically recommended unless the index of suspicion is high. Persistent fevers and/or ongoing positive blood cultures despite catheter removal strongly suggest the presence of metastatic foci of infection. The diagnostic evaluation to identify those foci should be guided by localizing signs and symptoms.

Other important manifestations of intravascular device-associated infections include skin and soft tissue involvement at the catheter exit site, the catheter tunnel tract, and the subcutaneous pocket of implanted devices (Table 29.1). Local infections typically present with erythema, induration, and/or tenderness. Serosanguinous or frankly purulent material may collect at the exit site. Exit-site infections are defined by the presence of signs or symptoms within 2 cm of the catheter exit site. Tunnel-tract infections are defined by the presence of signs or symptoms more than 2 cm from the catheter exit site along the subcutaneous tract of the tunneled catheter. Pocket infections are associated with signs of localized inflammation over the subcutaneous pocket where the reservoir of the device sits. Accumulation of infected fluid may result in spontaneous rupture and drainage to the surface or with necrosis of the overlying skin [4, 8, 14, 15]. Localized signs of acute inflammation can be subtle or absent during catheter exit-site infections in patients with neutropenia. At times, the only hint that a neutropenic patient has a pocket infection comes when the surgeon who is asked to remove the infected device observes unhealthy-appearing subcutaneous tissue in the area where the reservoir was located. The findings can be quite subtle. It is important to note that localized signs of skin or soft tissue inflammation are absent in most cases of CRBSI because the vast majority of those infections involve only the distal segment of the catheter [16].

**Table 29.1** Types of central line infections

| Type of infection | Clinical characteristics |
|---|---|
| Exit-site infection | Erythema, induration, and/or tenderness within 2 cm of the catheter exit site |
| Tunnel-tract infection | Erythema, induration, and/or tenderness >2 cm distal to the catheter exit site |
| Pocket infection | Erythema, induration, fluid accumulation, and/or tenderness over the subcutaneous pocket where the reservoir of the device rests. Complications include rupture with drainage to the skin surface, phlegmon, and necrosis of the overlying skin |
| Catheter-related bloodstream infection (CRBSI) | Positive blood culture (at least one from the peripheral site), fever, and line malfunction. Complications include suppurative thrombophlebitis, septic pulmonary emboli, tricuspid and pulmonic valve endocarditis, and metastatic systemic infections of any tissue or organ |

### 29.3.2 Risk Factors

Risk factors associated with the development of catheter-associated infections can be divided into host-related problems and device-related issues.

Host factors that increase the risk for developing a catheter-associated infection:

- Immune deficiency, especially chemotherapy-induced neutropenia, bone marrow transplantation, and solid-organ transplantation [17–20]
- Receiving total parenteral nutrition (TPN) [20]
- Chronic illnesses, including diabetes, end-stage renal disease, and short-gut syndrome [21–23]
- Loss of skin integrity, particularly in patients with burn injuries [24, 25]

- Known colonization with certain organisms that are particularly virulent, most notably *S. aureus* [26]
- Extremes of age, including very-low-birth-weight (VLBW) infants [27, 28]

Device-associated factors that impact the risk for developing a catheter-associated infection:

- Anatomic site of catheter placement: risk of infection is highest for femoral vein catheters and lowest for subclavian catheters [29, 30]
- Type and placement of the device: risk is reduced by tunneling of CVCs and lowest with totally implantable devices [9, 31]
- Risk for infection increases with poor adherence to sterile barrier precaution procedures during catheter placement [32, 33]
- Risk for infection increases if the placement of the catheter is performed during a medical emergency [34]
- Risk for infection increases with the presence of moisture around the catheter exit site [35]



### 29.3.3 Diagnosis

The proper collection of blood cultures is crucial in making the diagnosis of CRBSI. The collection of an adequate blood volume is the most important factor impacting the ability to identify bacteremia or fungemia [36, 37]. When CRBSI is suspected, blood samples of the same volume should be obtained from a peripheral vein and from each lumen of the intravascular catheter before empiric antibiotic therapy is initiated [38]. Two or more blood cultures that are positive for the same organism, collected from both a peripheral vein and from the intravascular device, are generally required for diagnosis of CRBSI. If the decision is made to remove the catheter, quantitative and semiquantitative culture of the catheter tip or the material inside the port reservoir have been used to confirm the diagnosis [39], although recent literature suggests these methods may not offer substantial benefit [40, 41].

- In the semiquantitative catheter tip culture method, a segment of the catheter tip is rolled across a blood agar plate in an attempt to detect the presence of bacteria on the outside of the catheter. A positive result is defined as the growth of 15 or more colonies of bacteria (colony-forming units, or CFU) [42].
- In the quantitative catheter tip culture method, intradermal and intraluminal segments of the catheter are immersed in culture broth and sonicated. Standard volumes of broth are inoculated onto solid culture media allowing for estimation of the burden of microorganisms in each of the samples. The threshold for a significant colony count is $10^3$ CFU/mL [43–46].

Blood cultures have high negative predictive value for CRBSI [47]. On the other hand, positive cultures must be interpreted carefully because some of the common etiologies of CRBSI are also common blood culture contaminants, especially coagulase-negative *Staphylococcus* species and *Enterococcus* species (Table 29.2). In addition, catheter hubs are often colonized with bacteria [48, 49]. As such, contamination of blood cultures may occur especially when the catheter hub is not thoroughly decontaminated before blood is collected [50]. The fairly common practice of collecting standard blood cultures from central catheters rather than from peripheral veins is discouraged. Whether the intention is for convenience or to spare the patient a peripheral needle stick; if a CRBSI is not suspected, standard broth bottle blood cultures should be collected from a peripheral vein, where the skin preparation and blood collection technique are far less likely to lead to a false-positive culture because of inadvertent contamination. Quantitative and semiquantitative catheter tip cultures described above are well-documented methods for confirmation of CRBSI but don't allow for the catheter to be retained in an attempt to clear the infection medically. In addition, not all microbiology laboratories are equipped to efficiently process quantitative cultures [51]. Alternatively, differential time to positivity, where time to growth is compared between blood cultures of the same volume collected from different sites (e.g., CVC and a peripheral site), has been increasingly used [52–54]. The differential time to positivity method is based on the theory that blood samples that contain higher densities of bacteria

**Table 29.2** Etiologies of monomicrobial catheter-related bloodstream infections in a large surveillance study that evaluated more than 24,000 cases of BSI [18][a]

| Pathogen | Percentage (%) |
|---|---|
| Gram-positive bacteria | 65 |
| Coagulase-negative *Staphylococcus* species | 31 |
| *Staphylococcus aureus* | 20 |
| *Enterococcus* species | 9 |
| Other gram-positive bacteria | 5 |
| Gram-negative bacteria | 25 |
| *Escherichia coli* | 6 |
| *Klebsiella* species | 5 |
| *Pseudomonas* species | 4 |
| *Enterobacter* species | 4 |
| *Serratia* species | 2 |
| *Acinetobacter* species | 1 |
| Other gram-negative bacteria | 3 |
| *Candida* species | 9 |
| Anaerobes | 1 |

[a]Polymicrobial infections accounted for 13% of the infections in this large study

will grow faster in the laboratory and therefore be detected earlier by the automatic culture systems. Using the differential time to positivity method, CRBSI is likely when the blood culture drawn from the intravascular device is flagged positive at least 2 h before growth is detected from the peripheral blood culture [55].

### 29.3.4 Etiologies

Coagulase-negative *Staphylococcus* species, such as *S. epidermidis*, are the most common causes of CRBSI, although *S. aureus*, *Enterococcus* species, Gram-negative enteric bacilli, and *Candida* species are also seen regularly (Table 29.2) [18, 56, 57].

### 29.3.5 Treatment

If the clinical suspicion is high for a CRBSI, appropriate blood cultures should be collected and empiric antibiotic therapy administered. Choosing an empiric antibiotic treatment regimen rests on several considerations, including the most likely microbiologic causes, the severity of the acute febrile illness, the patient's underlying medical conditions, and the degree of immunocompromise, if any. Vancomycin is typically included in the empiric regimen since the majority of CRBSIs are caused by coagulase-negative *Staphylococcus* species and other Gram-positive organisms [8]. Addition of a second antimicrobial agent with broad-spectrum activity against Gram-negative bacilli including *Pseudomonas* species is appropriate in many settings, especially for immunocompromised hosts and patients presenting with signs of sepsis. Circumstances where infection with *Candida* species is more common include a catheter with a femoral vein insertion site, catheters used for infusions of total parenteral nutrition, prolonged use of broad-spectrum antibiotics, hematologic malignancy, receipt of bone marrow or solid-organ transplant, or heavy colonization or mucous membrane infection with yeast. The addition of empiric antifungal therapy should be considered under any of these circumstances until candidemia has been ruled out. An echinocandin or azole class medication would be most appropriate [8, 58].

The initiation of empiric anti-infective therapy in patients with suspected CRBSI is important, but doing so does not reduce the importance or urgency of considering removal of the device in question. As with any foreign body contamination (infection), the single most effective intervention leading to cure of a CRBSI is removal of the catheter. Doing so is not always practical, so in lower-risk circumstances, efforts to retain and treat the infection with antibiotics alone are attempted. When this management pathway is chosen, frequent reassessments are needed so that signs of treatment failure can be identified swiftly and arrangements can be made for catheter removal. Catheters should be removed promptly if the patient has severe sepsis, hemodynamic instability, suppurative thrombophlebitis, or endocarditis or already has evidence for hematogenous seeding of other sites [▶ Call Out Box 29.1 and 29.2]. In addition, catheter removal should be performed as soon as feasible for any CRBSI caused by *S. aureus*, *Pseudomonas aeruginosa*, *Mycobacterium* species, and any yeast or mold, including *Candida* species, because local and systemic complications are common and are often severe and line salvage, even after prolonged courses of antimicrobial treatment, is extremely unlikely [8, 10, 59–63]. Catheter removal is also indicated when blood cultures continue to be positive despite more than 72 h of antimicrobial therapy to which the organism is susceptible.

Patients with tunnel-tract infection or port abscess should have their catheters/devices removed, while uncomplicated and mild exit-site infections can often be treated with topical antimicrobial agents without catheter removal; however, if an exit-site infection does not respond to topical therapy or if it is associated with purulent drainage, then systemic antibiotics are indicated. The catheter should be removed if systemic therapy fails [8, 22].

The treatment duration for CRBSI depends on the causative organism, whether the catheter has been removed and whether features of complicated CRBSI are present (Table 29.3). When the catheters are removed in uncomplicated CRBSI cases, recommended treatment duration is between 5 and 14 days, depending on the causative organism and clinical condition of the patient. In contrast, when complicated CRBSI occurs, the length needed to treat the

**Call Out Box 29.1**
**Clinical indications for device removal in patients with catheter-related bloodstream infections:**
- Severe sepsis
- Hemodynamic instability
- Suppurative thrombophlebitis
- Endocarditis
- Metastatic infection
- Tunnel-tract infection
- Port pocket infection
- Exit-site infection not responding to antibiotic therapy
- Persistent positive blood cultures despite more than 72 h of antimicrobial therapy to which the causative organism is susceptible

**Call Out Box 29.2**
**Microbiologic indications for device removal in patients with catheter-related bloodstream infections: *Catheters that are infected with the following pathogens should always be removed as soon as feasible:***
- *Staphylococcus aureus*
- *Pseudomonas aeruginosa*
- Multidrug-resistant Gram-negative enteric bacilli
- *Mycobacterium* species
- Fungi, including *Candida*, and other species of yeast
- *Bacillus* species, *Micrococcus* species, *Propionibacterium* species if infection is comfirmed

**Table 29.3** Management of long-term central venous catheter- and totally implantable device-related bloodstream infections based on the microbiologic etiology

| Etiology | Remove device? | Preferred antimicrobial options | Length of antibiotic therapy |
|---|---|---|---|
| Coagulase-negative *Staphylococcus* species | Not unless there is another indication to do so | Penicillinase-resistant penicillin (nafcillin or oxacillin) if methicillin susceptible<br>Vancomycin if methicillin resistant | If line retained: 10–14 days of IV and lock therapy<br>If line removed and no complication: 5–7 days IV<br>If complications present: remove line and treat accordingly |
| *Staphylococcus aureus* | Yes | Penicillinase-resistant penicillin (nafcillin or oxacillin) if methicillin susceptible<br>Vancomycin if methicillin resistant<br>Daptomycin if vancomycin MIC ≥2 μg/ml | 14 days if patient is not diabetic, is not immunosuppressed, has no prosthetic intravascular devices, and has no complications<br>May require as long as 4–6 weeks |
| *Enterococcus species* | Not unless there is another indication to do so | Ampicillin or penicillin plus aminoglycoside, if susceptible<br>Vancomycin replaces ampicillin for ampicillin-resistant isolates<br>If ampicillin and vancomycin resistant, consider linezolid or daptomycin | If line retained: 7–14 days of IV and lock therapy<br>If line removed and no complication: 7–14 days IV<br>If complications present: remove line and treat accordingly |
| *Micrococcus* species, *Bacillus* species, *Propionibacterium* species | Yes if ≥2 blood cultures are positive | Vancomycin or a beta-lactam class antibiotic depending on susceptibility results | Remove line, 7–14 days of IV antibiotics |
| *Pseudomonas species* | Yes | Anti-pseudomonal agent to which the isolate is susceptible such as ceftazidime, cefepime, imipenem, meropenem, piperacillin plus tazobactam with or without an aminoglycoside | Remove line and treat with 7–14 days of IV antibiotics |
| Other Gram-negative enteric bacilli | Typically removed | Depends on species and antimicrobial susceptibility results. Catheters that are infected with multidrug-resistant isolates should be removed promptly | Remove line and treat with 7–14 days of IV antibiotics<br>If line retained: 10–14 days of IV and lock therapy<br>If complications are present, remove catheter and treat accordingly |
| *Candida* species | Yes | Echinocandin class or azole class antifungal medication | Remove line, treat with antifungal for 14 days if no complications |

*ESBL* extended-spectrum beta-lactamase, *IV* intravenous, *MIC* minimum inhibitory concentration

complication dictates the duration of anti-infective therapy. In addition, if bacteremia or fungemia persists after catheter removal for more than 72 h, prolonged antibiotic therapy (4–6 weeks) is recommended, particularly in the settings of *S. aureus* and *Candida* species CRBSI.

Attempts to salvage infected catheters with treatment regimens that allow the device to be retained are reasonable in certain circumstances. Curing a catheter-associated bloodstream infection without removing the catheter poses some obvious risks. If eradication of the pathogen is delayed, the formation of thrombi and/or the metastatic seeding of the infection to distal sites can quickly change an uncomplicated problem to one that requires removal of the catheter anyway, along with an extended duration of treatment. Some catheter infections recur days to a few weeks after a course of antibiotics was thought to successfully cure them without removing the device. Such risks should be discussed with the patients so that they may participate in early management decisions.

The approach of using a combination of systemically administered antibiotics together with "lock" therapy has gained recent attention with the hope of achieving higher rates of success in retaining infected catheters [59, 64]. Lock therapy involves instilling ethanol or a highly concentrated antimicrobial solution into the infected catheter lumen(s) and allowing the solution to dwell for extended periods of time. The duration of lock therapy is typically the same as the systemic antibiotic therapy. While this approach should theoretically lead to improved catheter salvage rate, data on efficacy have been inconclusive [59, 65–67].

## 29.4 Prevention of Central Line-Associated Bloodstream Infections

Given the substantial healthcare burden associated with CLABSI, prevention is of paramount importance [4–6]. The "bundle" approach, where a group of interventions are implemented simultaneously, has proven quite successful in the prevention of CLABSI [7, 68–70]. While the specific individual items included in a "bundle" vary from institution to institution, they generally involve implementing standard operating procedures related to precautions and interventions during and after catheter insertion. At the time of catheter insertion, compliance with hand hygiene protocols, adherence to sterile techniques, the use of maximal barrier precautions, the use of chlorhexidine-containing antiseptics, choosing the optimal insertion site, and the use of sterile dressings are typically included. For the maintenance of catheter integrity after insertion, meticulous adherence to hand hygiene protocols and aseptic technique with ongoing assessments for the necessity of the catheter are generally included. The timely removal of catheters that are no longer medically necessary should be included as a best practice recommendation whenever a bundled standard operating procedure is developed.

Antibiotic locks and 70% ethanol locks have been studied as infection prevention measures in various settings [71–76]. Many of these studies show reduced incidence of CRBSI associated with lock therapy. Some randomized trials, however, failed to show efficacy of this approach in the prevention of CRBSIs. Moreover, the theoretical concerns regarding the potential emergence of antibiotic resistance during antibiotic lock prophylaxis lend controversy to the approach explaining why it has not become a universal approach in developing bundles [77, 78]. Currently, the use of prophylactic antimicrobial lock is only recommended as an addition to other bundle strategies in patients with long-term catheters or totally implanted devices with reservoir ports who have already demonstrated a history of multiple CRBSI [7].

### Case Study

#### Practical Examples

**Case 1**

A 6-week-old infant who was born at 25 weeks' gestational age develops fever and episodes of apnea during his birth hospitalization. He has been receiving total parental nutrition via a PICC that was placed 18 days ago. Blood and urine cultures were collected and broad-spectrum empiric antibiotic treatment initiated. The blood cultures collected from the PICC were positive for the growth of *Pseudomonas aeruginosa* and indicative of a catheter-associated infection. The PICC was removed and the empiric antibiotic regimen changed to cefepime, based on the antibiotic susceptibility results. A repeat blood culture that was collected 48 h later was negative. Treatment with cefepime was continued for 10 days from the time of the negative culture. The subsequent blood culture was negative, so it would also be acceptable to count the total days of effective antibiotic therapy starting from the day that the catheter was removed.

**Case 2**

A 58-year-old woman with acute myeloid leukemia who underwent autologous bone marrow transplantation 2 weeks ago developed fever of 40 °C. A subcutaneous port device was placed 4 months ago to facilitate her treatment. She has been receiving antibiotic prophylaxis with levofloxacin during this pre-engraftment period. Her only complaint is fever and chills. A source for the fever is not identified on physical examination. The skin overlying her intravascular catheter device appears normal. Empiric broad-spectrum antibiotics are administered after blood and urine cultures are collected. The next day, blood cultures drawn from both the catheter and from a peripheral vein were flagged as positive for the growth of Gram-negative rods. You note that the culture collected from the catheter was flagged as positive 6 h before the peripheral culture was. The time differential strongly suggests a CRBSI. All of the blood culture isolates are identified as *Escherichia coli*, resistant to quinolone class antibiotics but susceptible to ceftriaxone. Since she is clinically stable, a decision is made to attempt to salvage her catheter device rather than remove it. Antibiotic lock therapy and intravenous ceftriaxone are administered for 14 days. The patient remained fever-free during and after the antibiotic treatment course. Repeat blood cultures showed no growth. The infection did not recur indicating successful medical treatment with salvage of the catheter device.

**Case 3**

A 45-year-old man undergoing hemodialysis for end-stage renal disease presents with low-grade fever and malaise during one of his dialysis sessions. A blood culture from the hemodialysis catheter was positive for growth of a *Bacillus* species. The provider, recognizing that the *Bacillus* species could be either a contaminant or a cause of CRBSI, collected new cultures from the catheter and from a peripheral vein. The repeat cultures were also positive for the growth of *Bacillus* species. The hemodialysis catheter was then removed and the patient treated with 10 days of intravenous vancomycin before a new dialysis catheter was placed.

A 17-year-old boy with short-gut syndrome has been dependent on total parenteral nutrition since infancy. Currently, his intravenous nutrition is administered via a long-term central venous catheter that was placed nearly 3 years ago when his prior catheter malfunctioned. One day ago, the patient noticed a red swollen and slightly tender area on his chest wall "an inch or so" from the catheter entry site. On physical examination, he appears well. There is no fever. Erythema and induration are noted overlying the tunneled portion of the catheter 3.7 cm medial to the catheter exit site. Blood cultures are collected, and he is treated empirically with broad-spectrum antibiotics. Since there is a high suspicion for a tunnel-tract infection, the catheter is removed the next day. All blood cultures remained negative. A semiquantitative catheter tip culture was positive for the growth of 25 CFU of methicillin-susceptible *Staphylococcus aureus*. Oral antibiotics would usually be appropriate for the treatment of this infection, but the patient under discussion requires parenteral therapy since he would not absorb medications taken by mouth. He is treated with intravenous cefazolin for 10 days. The antibiotic and parenteral nutrition are both administered via peripheral intravenous catheters. Following successful treatment for the tunnel-tract infection, he is scheduled for placement of a new long-term central catheter.

## 29.5 Exercises

Please refer to the supplementary information section for answers to these exercises.

Case 1. A 64-year-old woman with history of hypertension presents with chest and back pain subsequently diagnosed as an ascending aortic dissection. She undergoes urgent surgical repair of the ascending aorta. A right internal jugular central venous catheter is placed in the operating room. She has a relatively stable postoperative recovery course in the intensive care unit until she develops fever and hypotension 4 days later. There is no significant change in her chest radiograph. There is no erythema around the exit site of the central venous catheter. Urine culture shows no growth. Blood cultures drawn from a peripheral vein show the growth of Gram-positive cocci in clusters at 22 h of incubation, and blood cultures from the central line show the growth of Gram-positive cocci in clusters at 19 h of incubation.

- *What is the next step in treating this infection? What is your empiric antibiotic choice?*
- *The blood culture isolates are determined to be methicillin-susceptible Staphylococcus aureus. Should any changes be made with the antibiotic treatment?*
- *How long should this infection be treated?*
- *What if her bacteremia persists despite intravenous antibiotics and removal of the catheter?*

Case 2. A 6-year-old boy with history of acute lymphoblastic leukemia undergoing consolidation chemotherapy is brought into the emergency room with fever. His vital signs are otherwise stable. He does not have cough, vomiting, or diarrhea. He has a totally implanted central venous catheter. The skin overlying the device appears normal. His absolute neutrophil count is 300 cells/μl.

- *What should you do?*
- Blood cultures drawn from the subcutaneous port and the peripheral site are both positive for the growth of *Staphylococcus epidermidis. What is your next step? What is your antibiotic choice?*
- *Would your management change if blood cultures collected from the catheter collected 24, 48, and 72 h after the vancomycin was started were still positive?*

Case 3. A 3-week-old, born at 24 weeks' gestational age, has had multiple serious medical complications of extreme prematurity including necrotizing enterocolitis. The infant receives total parenteral nutrition via a PICC. His nurse notes an increased frequency of apnea and bradycardia episodes associated with hypothermia. Blood and urine cultures are collected. A complete blood count shows leukocytosis and thrombocytopenia. Empiric treatment with vancomycin and cefepime is started. Despite treatment with broad-spectrum antibiotics, he requires several boluses of isotonic crystalloid and inotropic support to maintain his perfusion.

- *What do you suspect as the reason for his lack of improvement?*
- *How would you treat this infection?*
- *Additional diagnostic tests should be done to evaluate for possible disseminated infection. What tests should be included?*

## 29.6 Summary

- The presence of fever in a patient who has an indwelling intravascular device should prompt suspicion for CRBSI. The initial evaluation should include an examination of the skin at and surrounding the catheter site. Blood cultures collected from a peripheral vein and from the catheter should include quantitative cultures where available. Clues obtained from the medical history and physical examination should direct the approach used to evaluate for other possible sources of fever.
- When treating patients with CRBSI, persistent bacteremia and/or unrelenting fever despite antibiotic treatment and catheter removal suggests the presence of a suppurative complication such as thrombophlebitis, tunnel infection with abscess formation, endocarditis, or metastatic spread to a distant anatomic site.
- Quantitative blood cultures that compare the number of colony-forming units of bacteria from equal volumes of blood collected from a peripheral vein and from the catheter are quite helpful in identifying the source of the bacteremia. Differential time to positivity of blood cultures obtained from a peripheral vein and from the catheter lumen(s) has recently gained popularity as a diagnostic tool for CRBSI.
- Catheter salvage can be considered in select uncomplicated cases of CRBSI. In every instance where an infected catheter is being retained in an attempt to sterilize rather than remove it, a high level of vigilance must be maintained. The attempt to salvage a catheter should be aborted, and the catheter is removed the moment a complication emerges or is highly suspected.
- CRBSI accounts for a substantial healthcare burden. Prevention is of paramount importance. "Bundle" approaches have been used with great success.

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## Further Reading

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## Related Links to Journals, Books and/or URLs

http://www.idsociety.org/Guidelines/Patient_Care/IDSA_Practice_Guidelines/Other_Guidelines/Other/Management_of_Catheter-related_Infections/.
CDC prevention recommendations.

# Osteomyelitis and Septic Arthritis

## Fever and Limp

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**Learning Objectives**

- Apply the knowledge of the most common bacterial etiology of osteomyelitis and septic arthritis to develop an empiric treatment plan.
- Generate a pathogen-specific differential diagnosis for osteomyelitis and septic arthritis based on the patient's age.
- Summarize the risk factors for the development of chronic sequelae following osteomyelitis or septic arthritis.



## 30.1 Introduction to the Problem

Osteomyelitis and septic arthritis have a reported incidence ranging between 8 and 13 per 100,000 population. Infection typically results from bacterial seeding of the bone and/or joint space during a primary bacteremia, although blood cultures are positive in only 40–50% of cases. Less common routes to osteomyelitis and septic arthritis include traumatic injury with environmental wound contamination, penetrating trauma, chronic deep decubitus ulcer, and internal and external hardware following open reduction and internal fixation of a fracture or prosthetic device implantation. Osteomyelitis may occur in conjunction with septic arthritis. This is particularly common among children under 18 months of age who develop septic arthritis because of age-dependent persistence of bridging blood vessels across the epiphysis and the physis. These trans-epiphyseal vessels ultimately obliterate around the age of 18 months. Severe bloodstream infections may seed multiple bones and/or joints. Multifocal bacterial osteomyelitis is most typically seen in the setting of prolonged bacteremia with *Staphylococcus aureus*.

## 30.2 Definitions

**Osteomyelitis** - is technically defined as inflammation of the bone but when the term is used without further descriptors is generally accepted to indicate a bacterial infection of the bone. Fungal osteomyelitis is uncommon. Chronic recurrent multifocal osteomyelitis (CRMO) is a rare noninfectious inflammatory condition that mimics bacterial osteomyelitis.

**Septic arthritis** - refers to infections of the joint space. Bacterial infections predominate, but fungi may also cause infection.

## 30.3 Basic Concepts

### 30.3.1 Osteomyelitis

More than half of all cases of acute hematogenous osteomyelitis occur in children less than 5 years of age. With the exception of the first year of life, males are twice as likely to develop osteomyelitis when compared to females. Although recent minor trauma is frequently described during the patient interview, there is no clear correlation between such trauma and the development of acute hematogenous osteomyelitis. Patients with osteomyelitis typically present with abrupt onset of symptoms including fever and pain, swelling, and erythema of the affected site. The vast majority of bone infections are localized to a single site. Published case series indicate that the distal femur and the proximal tibia consistently vie for the most common location of bone infection. Other long bones, such as the humerus, are also commonly infected. Osteomyelitis of the pelvis and vertebral bodies occurs less commonly and tends to be more difficult to recognize clinically because the patient is more inclined to complain of vague diffuse pain in the general area of infection rather than describing the point tenderness of a long bone. Objective findings on physical examination may be quite subtle. As such, it is important to pay close attention to diagnostic clues during the history and physical examination and to maintain a level of suspicion for bone infection in a patient with fever and pain even in the absence of localizing signs.

### 30.3.2 Septic Arthritis

The incidence of acute hematogenous septic arthritis peaks before 3 years of age, although it occurs in all ages. Bacteremia is identified in approximately 40% of cases, and synovial fluid culture is positive in approximately 60%. Patients generally present with fever, pain, decreased range of motion, and reluctance or refusal to move the joint. Edema and erythema of the affected area are also typical. Young children who present with a septic hip joint may not have abnormalities noted on visual inspection. A clue to the diagnosis in this setting is the observation that the child is holding the hip in an abducted, externally rotated position with the knee flexed (e.g., frog leg position). This is a position of comfort when the hip joint capsule is swollen and inflamed. Any active or passive movement away from this position elicits exquisite pain.

The anatomic site most frequently infected is the knee joint followed by the hip, ankle, and elbow joints. When a septic joint is suspected based on a patient's history and physical examination findings, a joint aspiration should be performed for diagnostic purposes. Synovial fluid analysis should include cell count and differential Gram stain and bacterial culture. Some joint infections require surgical intervention for drainage and washout to adequately remove purulent fluid from the joint space, alleviate joint pressure, and reduce the possibility of further joint damage. Septic arthritis of the hip is considered a surgical emergency because of the risk for developing avascular necrosis of the femoral head from comprised arterial blood supply caused by intra-articular swelling and resultant pressure. All septic hip joints require an open surgical procedure [► Call Out Box 30.1].

**Call Out Box 30.1**

Septic arthritis of the hip joint is a surgical emergency. Open arthrotomy is necessary to reduce the risk for developing avascular necrosis of the femoral head. The open surgical procedure immediately reduces the pressure in the joint capsule, preserving arterial blood flow.

### 30.3.3 Differential Diagnosis

The differential diagnosis of acute osteomyelitis and septic arthritis is broad. Malignancy should be considered. The clinical presentation of primary bone tumors such as osteosarcoma and Ewing sarcoma, leukemia, primitive neuroectodermal tumors, and neuroblastoma can all cause substantial bone pain, and sometimes that pain can be quite localized. Non-oncologic possibilities include inflammatory conditions such as chronic recurrent multifocal osteomyelitis, polyarteritis nodosa, serum sickness, and transient synovitis. Transient synovitis is sometimes erroneously referred to as "toxic synovitis," but there is nothing "toxic" about it. The condition is much more common than septic arthritis, occurring primarily among children between 4 and 10 years of age. Children with transient synovitis typically present with a history of a recent upper respiratory tract infection and pain in the affected joint, most often a knee or hip. An important diagnostic clue that helps to differentiate transient synovitis from septic arthritis is the absence of fever. Children with transient synovitis may have joint swelling, but erythema and warmth are not prominent features, and while many have an antalgic gait (limp), they are unlikely to completely refuse weight bearing activities compared to children with septic arthritis. Transient synovitis is also distinguished from septic joint by prompt response to nonsteroidal anti-inflammatory agents.

In Lyme-endemic areas, or in patients who have traveled to Lyme-endemic areas, monoarticular large joint arthritis is a common presentation of late-stage Lyme disease. Synovial fluid analysis may reveal abnormalities similar to those seen with early septic joints, although the Gram stain and culture will be negative. Serologic testing for Lyme disease will reveal the cause of the joint inflammation.

Chronic recurrent multifocal osteomyelitis (CRMO), a noninfectious inflammatory disease, presents with fever and bone pain. The bone pain is often unifocal on initial presentation, and magnetic resonance imaging reveals findings typical for osteomyelitis. Blood and bone cultures (if obtained) are negative. This exact scenario is seen in approximately half of patients who develop acute hematogenous osteomyelitis, so it's no surprise that almost every patient ultimately diagnosed with CRMO is treated empirically, at least once, for a bacterial bone infection. Patients with CRMO are typically older than those who develop bacterial osteomyelitis, with a median age of 10 years. Features that help to distinguish CRMO from bacterial osteomyelitis include uniformly negative blood and bone cultures (when obtained), the presence of inflammation in bones that don't typically develop bacterial infections, such as the clavicle, and/or the presence of inflammation involving multiple bones simultaneously. Finally, patients with CRMO may have silent lesions that are identified on whole body MRI, bone scan, or skeletal survey, which may help to differentiate infection from CRMO early on. Up to one-quarter of children with CRMO will eventually be diagnosed with another associated inflammatory disorder such as plantar-palmar pustulosis, psoriasis, or Crohn disease.

### 30.3.4 The Pathogens that Typically Cause Osteoarticular Infections

The most common pathogen to cause infection of the bones or joints is *S. aureus*, but depending on the age of the patient, other organisms may be more common (Table 30.1). Both methicillin-susceptible *S. aureus* (MSSA) and methicillin-resistant *S. aureus* (MRSA) are commonly seen. *Streptococcus pyogenes*, *Kingella kingae*, and *Streptococcus pneumoniae* are other relatively commonly encountered organisms. Infection with *K. kingae* often occurs following a viral upper respiratory tract infection. The organism is a normal human oropharyngeal flora, so the inflamed upper respiratory tract may represent the portal of entry for this organism for hematogenous spread to the bones or joints. Nasal colonization of *K. kingae* is close to 30% in those who attend daycare. Emerging data suggest that when special attention is taken to culture this somewhat fastidious organism, or when non-culture techniques are used to identify it, *K. kingae* may be the most frequent cause of osteomyelitis and septic arthritis in toddlers.

Uncommon bacterial pathogens known to cause osteoarticular infections include *Bartonella henselae*, *Haemophilus influenzae*, coagulase-negative staphylococci, *Cutibacterium acnes*, enteric Gram-negative bacilli including *Salmonella* species, and anaerobic pathogens. Specific risk factors for developing these unusual causes of bone or joint infection are shown in Table 30.2. Among anaerobes, *Actinomyces* species have an unusual proclivity to cause bone infections. Fungal organisms are rare causes of osteoarticular infections. Risk factors for fungal osteoarticular infections include penetrating trauma involving plant material, neonatal age (*Candida* species), living or traveling to areas where dimorphic fungi are endemic, prolonged neutropenia (*Aspergillus*

**Table 30.1** Common pathogens causing acute hematogenous osteomyelitis and septic arthritis by age

| Age | Pathogens |
|---|---|
| Neonates and young infants (Birth to 2 months) | *Streptococcus agalactiae* (group B streptococcus)<br>*Escherichia. coli* and other enteric Gram-negative rods<br>*Staphylococcus aureus*<br>Coagulase-negative staphylococci<br>*Candida* species |
| Infants and toddlers (2 months to 3 years) | *S. aureus*<br>*Kingella kingae*<br>*Streptococcus pyogenes* (group A streptococcus)<br>*Streptococcus pneumoniae* |
| Children (3–11 years) | *S. aureus*<br>*S. pyogenes* |
| Adolescents and adults | *S. aureus*<br>*S. pyogenes*<br>*Neisseria gonorrhoeae* |

**Table 30.2** Risk factors that predispose individuals to osteoarticular infections caused by common and unusual pathogens

| Risk factor | Pathogen |
|---|---|
| Indwelling hardware | *S. aureus*<br>Coagulase-negative staphylococci<br>*Cutibacterium acnes* |
| Unimmunized child | *H. influenzae* type b |
| Cat or kitten exposure | *Bartonella henselae*<br>*Pasteurella multocida* |
| Traveling or residing in an endemic area | *Mycobacterium tuberculosis*<br>*Histoplasma capsulatum*<br>*Blastomyces dermatitidis*<br>*Coccidioides immitis* |
| Penetrating trauma | A variety of opportunistic organisms including fungi |
| Dental caries | *Actinomyces* species (lumpy jaw) |
| Underlying hemoglobinopathy | *S. aureus*<br>*Salmonella* species<br>Enteric Gram-negative organisms<br>*S. pneumoniae*<br>*H. influenzae* type b |
| Prolonged neutropenia, primary neutrophil defect | *Aspergillus* species<br>Other opportunistic molds |

species), and primary defects in neutrophil function (Table 30.2). Tuberculous osteomyelitis occurs in approximately 1% of patients with *Mycobacterium tuberculosis* infection, but unlike other causes of bone infection, the most common bony site for tuberculosis is the vertebrae. Chronic, destructive vertebral osteomyelitis was described by Percivall Pott in 1799, 71 years before *M. tuberculosis* was discovered. Tuberculosis of the spine is still referred to as Pott's disease today.

### 30.3.5 Diagnostic Laboratory Evaluation

Blood cultures are an important component of the diagnostic evaluation in the setting of suspected bone and/or joint infection. A positive blood culture allows the isolate to undergo antibiotic susceptibility testing so that empiric therapy can be changed to targeted antibiotic therapy. Cultures from the bone and/or joint should also be obtained when feasible because doing so increases the chances of recovering a microbiologic isolate. Complete blood counts are often obtained as a part of the diagnostic evaluation. The total white blood cell (WBC) count and the percentage of polymorphonuclear cells seen on the differential are typically elevated during acute bacterial infection, but these findings are nonspecific. While an elevated WBC count showing a predominance of polymorphonuclear cells raises the clinical suspicion of an acute bacterial infection, their absence does not eliminate the possibility of a bacterial bone or joint infection. The platelet count is also often elevated, a finding that can be viewed as a nonspecific marker of systemic inflammation. Other inflammatory biomarkers, such as the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), are often assessed during the initial diagnostic evaluation. The CRP is almost uniformly elevated in the acute setting of bacterial infection. One to two days after the appropriate interventions (effective antibiotic therapy with or without surgery) have been initiated, the CRP should begin to decline, generally reaching a normal level over the course of 1–2 weeks. In contrast, the ESR tends to increase further during the first several days of effective intervention before it begins to decline [▶ Call Out Box 30.2]. Both tests may be used as indirect measures of the response to therapy. Failure of empiric therapy may occur when a microbiologic isolate was not recovered but is resistant to the chosen antibiotic. The failure to respond to treatment with antibiotics might also be explained by the presence of an abscess that requires surgical intervention or the presence of a bone infarction with impaired blood supply to the area of infection. Without adequate blood supply to the infected bone, antibiotics cannot adequately reach the site where they are needed. It is important to consider each of these possibilities in a patient who appears to be failing antibiotic therapy since the optimal change in management might require switching the antibiotic, surgically draining an abscess, or surgically removing fragments of the dead bone. Repeat magnetic resonance imaging is quite useful in evaluating a patient for the presence of an abscess of bony sequestration. If neither are obvious, the antibiotic regimen should be changed with subsequent close monitoring of the patients symptoms and serial measurements of inflammatory biomarkers.

**Call Out Box 30.2**
The erythrocyte sedimentation rate (ESR), or "sed rate," is the rate at which red blood cells sediment by gravity over a period of 1 h. The laboratory result is reported as the millimeters of plasma present above the sedimented erythrocytes in a standard sized tube after 1 h (mm/h). A high number indicates that the cells fell to the bottom of the tube quickly. This occurs during conditions of acute inflammation because of the presence of inflammatory proteins, especially fibrinogen, that stick to the cells causing them to stack up in rouleaux formation. Individual erythrocytes sediment slowly, while stacked groups of cells sediment quickly resulting in an elevated ESR.

### 30.3.6 Radiologic Imaging

Magnetic resonance imaging (MRI) is the most sensitive (92–100%) radiologic test to identify bone and joint infections particularly when performed with gadolinium enhancement. MRI provides a high-resolution image of the bone marrow, the joint space, and the surrounding soft tissues. The technique is excellent for differentiating between

superficial soft tissue infections and deeper infections involving muscle and/or bone. MRI is also quite useful when evaluating a patient who has not had the expected response to treatment.

The sensitivity of technetium phosphate radionuclide scans (bone scans) in detecting a bacterial bone infection is between 80 and 100%. Abnormalities are visible on bone scan well before changes can be appreciated on plain radiographs. Bone scans can also be quite useful when CRMO or an oncologic process is high on the differential diagnosis, as it allows for a survey of the entire skeleton at once. Despite this advantage, bone scans are seldom used in the setting of suspected acute hematogenous osteoarticular infection, as they provide less detailed anatomic information compared to MRI, and are not helpful in determining a need for surgical intervention. Bone scans can be used during the evaluation of fever without localizing signs. If areas of increased signal uptake are identified, MRI or other higher-resolution imaging can be used to target the suspicious area to further define the inflammatory process detected by the bone scan.

Plain radiographs may show nonspecific changes during the first few days of illness, such as soft tissue swelling around the area of infection, but are more useful 10–20 days after the onset of the bone infection. Radiographic changes associated with periosteal new bone formation, periosteal elevation due to abscess formation, and erosion of the bony cortex or lytic lesions are not typically seen until at least 10 days have passed. Articular infections may reveal a widened joint space along with displacement of fat planes surrounding the joint. Infections that have been present for more than a month, bony sclerosis may be seen. Plain radiography is less expensive than MRI and bone scan, but does not provide sufficient detail, especially early on, to justify using it for diagnostic purposes. One notable exception is the use of plain radiography in the evaluation of suspected bacterial osteomyelitis in the newborn period. Bony erosions secondary to infection are seen on plain radiographs very early because the cortex is so thin at this age.

### 30.3.7 Treatment

Antimicrobial therapy is required in the treatment of bacterial osteomyelitis, but it is important to recognize that surgical intervention including irrigation and/or debridement may be necessary to control the infection. Surgical intervention is generally required in the setting of osteomyelitis complicated by the presence of a soft tissue abscess, subperiosteal abscess, necrotic bone, a foreign body, or heavy wound contamination. Septic joints should undergo arthrocentesis, and in the setting of septic hip, arthrotomy should always be performed. Surgical intervention allows for the collection of culture material directly from the involved site with a higher likelihood of organism identification for susceptibility testing and for improved antibiotic penetration into the infected area.

Antimicrobial therapy is initially empiric. The antibiotic choice is based on the age of the patient, known exposure history, presence of known risk factors, and local antimicrobial susceptibility profiles. *S. aureus* is the most common organism to cause osteoarticular infections, so empiric therapy should provide adequate antimicrobial coverage for that organism it. Knowing local antibiogram patterns is an important aspect of choosing empiric antibiotics, as different regions have distinct rates of methicillin-susceptible (MSSA) and methicillin-resistant *S. aureus* (MRSA) infections. Some areas also have high rate of clindamycin resistance for both MSSA and MRSA. In general, anti-staphylococcal penicillins (e.g., oxacillin or nafcillin) or first-generation cephalosporins (e.g., cefazolin) should be used when concern for MRSA is low. Clindamycin may be a good empiric choice when concern for MRSA is higher, but local resistance rates must be considered. In patients who present with a toxic appearance, vancomycin should be included as part of the treatment regimen from the start.

The typical length of therapy for uncomplicated acute hematogenous osteomyelitis is a minimum of 4 weeks. Uncomplicated septic arthritis is typically treated for 3 weeks. Therapy may be prolonged if the clinical response is slow or if the patient has a subacute (6–8 weeks) or chronic (8–12 weeks or longer) presentation before the diagnosis is made. In the setting of hardware-associated bone and joint infections, initial therapy may be as long as 6 months with chronic suppression thereafter unless and until all of the hardware can be removed.

The treatment of acute osteoarticular infections should always begin with intravenous antibiotic therapy. Transition from parenteral to oral therapy can be considered when the patient has defervesced, has shown good clinical response, and has declining inflammatory markers unless there are serious concerns about adherence. The microbiologic identification of the offending pathogen with subsequent antibiotic susceptibility results is also helpful in determining the timing and suitability of switching from parenteral to oral antibiotic treatment.

In special, higher risk circumstances, such as in neonates and in patients with sickle cell disease and other hemoglobinopathies, broader-spectrum antimicrobial coverage that includes Gram-negative organisms is prudent. This can be accomplished by using a third-generation cephalosporin (e.g., cefotaxime or ceftriaxone) along with the selected anti-staphylococcal coverage.

Other immunocompromised hosts are at risk for infections caused by both the usual suspects and a long list of unusual pathogens. Fungi, such as *Aspergillus* species, are well-known causes of bone infection in patients with prolonged, severe neutropenia and in the setting of bone marrow transplantation. Empiric therapy that includes voriconazole or another broad-spectrum antifungal agent may be warranted in certain situations. Finally, tuberculosis should be considered patients with vertebral osteomyelitis especially if they have a history of traveling to a country

known to be endemic for TB. In this setting, treatment includes four antituberculous medications for the first 2 months of therapy (typically rifampin, isoniazid, pyrazinamide, and ethambutol). If the *M. tuberculosis* isolate is available and known to be susceptible to isoniazid and rifampin, the four-drug regimen can be de-escalated to that two-drug regimen for at least 10 more months. If susceptibilities are not available, the four-drug regimen is used to complete the full 12 months of treatment.

### 30.3.8 Therapeutic Monitoring and Long-Term Sequelae



Osteoarticular infections require treatment for much longer durations than most other infections, so adverse drug reactions related to that prolonged therapy occur occasionally. Patients should be regularly monitored clinically and with appropriate laboratory testing so that any treatment-related side effects can be identified and addressed (Table 30.3).

The majority of patients with osteoarticular infection recovers without sequelae, however, as many as 25% percent of children with articular infection develop permanent consequences. Septic hip arthritis complicated by avascular necrosis of the femoral head leads to substantial morbidity. Chronic dislocation of the affected joint and varying degrees in loss of joint mobility and range of motion are also seen. Risk factors for the development of sequelae following septic arthritis are listed in ► Box 30.1. Long-term sequelae after acute hematogenous bone infection are uncommon but, when they do occur, are associated with substantial morbidity. Destruction of bony cortex results in a risk for developing a pathologic facture until bony remodeling can restrengthen the bony integrity. Pathologic fractures are most common in weight bearing bones, but can occur in any infected bone during the healing process. When osteomyelitis involves the area of a growth plate that has not yet fused, a resulting bone length discrepancy becomes obvious as the child grows. Prompt diagnosis and treatment with appropriate antibiotic therapy and any necessary surgical intervention are the critical components needed to reduce the risk for permanent sequelae.

**Table 30.3** Antibiotic-associated toxicities and recommended therapeutic monitoring during treatment for osteomyelitis and septic arthritis

| Antibiotic | Toxicities | Monitoring parameters |
|---|---|---|
| Beta-lactams<br>Oxacillin<br>Nafcillin<br>Ampicillin<br>Cefazolin<br>Others | Leukopenia<br>Neutropenia<br>Chemical hepatitis<br>Acute interstitial nephritis | Periodic laboratory testing to include complete blood count with differential, liver transaminases, and creatinine |
| Clindamycin | QTc prolongation<br>Leukopenia and thrombocytopenia<br>Renal dysfunction | Periodic electrocardiogram if receiving concomitant agents known to prolong QTc<br>Periodic laboratory testing to include complete blood count with differential and serum creatinine |
| Vancomycin | Leukopenia<br>Neutropenia<br>Ototoxicity<br>Nephrotoxicity | Periodic laboratory testing to include complete blood count with differential and creatinine<br>Vancomycin trough serum concentrations in patients receiving therapy for more than 48 h and in the setting of renal dysfunction<br>Monitor urine output |
| Linezolid | Pancytopenia<br>Thrombocytopenia<br>Lactic acidosis<br>Peripheral neuropathy<br>Visual changes | Periodic laboratory testing to include complete blood count with differential and serum lactate<br>Vision testing in patients receiving linezolid therapy greater than 3 months or with complaints of visual changes |
| Daptomycin | Myalgias<br>Arthralgias<br>Rhabdomyolysis<br>Renal dysfunction<br>Leukopenia | Periodic laboratory testing to include complete blood count with differential, liver transaminases, creatinine, and creatine phosphokinase (CPK) |
| Rifampin | Pancytopenia<br>Interstitial nephritis<br>Chemical hepatitis<br>Cholestatic jaundice<br>Be mindful of the many drug-drug interactions | Periodic laboratory testing to include complete blood count with differential, liver transaminases, bilirubin, creatinine |

**Box 30.1 Risk Factors for the Development of Permanent Sequelae Following Septic Arthritis**

- Bone infection adjacent to the infected joint
- Young age (less than 6 months)
- The affected joint is a hip or shoulder
- Delay in joint decompression
- Delay in the initiation of antibiotic therapy
- Persistently positive synovial fluid cultures
- Infections caused by *S. aureus* or an enteric Gram-negative rod

## 30.4 Summary

Osteoarticular infections are most commonly encountered in young children but also occur regularly in adults and patients with indwelling hardware and among those with certain underlying chronic diseases. *S. aureus* is the most common bacterial pathogen responsible for bone and joint infection. Empiric treatment of osteomyelitis and septic arthritis should target *S. aureus* with care to include coverage for *Kingella kingae* for children younger than 3 years of age. Local antibiotic susceptibility data should be taken into consideration when planning empiric antimicrobial therapy. Antibiotics are typically administered intravenously, at least until the patient has defervesced and shows other clear signs of improvement such as reduced pain. A transition from intravenous to oral agents can be considered in the vast majority of patients with uncomplicated infection. The length of therapy varies based on the duration of symptoms at presentation, the clinical course, and the specific pathogen but is typically 3–4 weeks for septic arthritis and 4–6 weeks for acute osteomyelitis.

**Case Study**

**Practical Examples**

1. A 20-month-old girl developeds fever to 39 °C for 2 days, associated with irritability and refusal to bear weight. On physical examination, she is noted to hold her right hip in a flexed and external rotation position. Laboratory evaluation reveals a total white blood count of 13,000 cells per microliter, a C-reactive protein of 12 mg/dL, and an ESR of 50 mm/h. Synovial fluid aspirated from her right hip reveals Gram-positive cocci in clusters. In addition to starting empiric anti-staphylococcal antibiotic therapy, this patient should undergo arthrotomy of the infected hip with drainage and irrigation. Septic hip arthritis always requires surgical intervention to reduce the potential for developing avascular necrosis of the femoral head.
2. A 7-day-old late preterm girl has been in the neonatal intensive care unit since birth. Her nurse expresses concern that the infant may have a nerve injury because the baby stopped moving her right arm. The infant appears well. In this setting, a diagnostic evaluation for possible osteoarticular infection, including radiographic imaging of the arm, is important because apparent paralysis that was not present at birth but develops later is more likely related to osteoarticular infection than nerve injury. When a newborn or young infant stops moving an extremity because of pain from an infection in a bone or joint, the condition is referred to as pseudoparalysis.
3. A 14-year-old boy stepped on a piece of wood while running barefoot around a creek behind his home. His mother promptly cleaned the wound and removed the visible foreign body. Several days following the injury, the patient developed midfoot swelling extending to the dorsal surface, associated with erythema and pain with ambulation. In this scenario, the presence of a retained foreign body is likely. Radiographic imaging should be performed to evaluate this possibility. Samples should be collected for bacterial and fungal cultures if possible, since a host of environmental opportunistic organisms could be present. If the infection does not respond promptly to treatment with empiric antibiotics, surgical exploration should be considered.
4. A 10-year-old boy develops mid-back pain with decreased mobility for a month. He describes low-grade fevers and night sweats for several weeks. During the medical history, you find that he emigrated from Mexico 6 months ago. His mother reports that the patient's uncle, who lives with them, has a chronic cough. On physical examination, the boy is unable to bend forward to touch his toes because as he attempts to flex his spine, his pain worsens. He has tenderness along his spine localized to thoracic vertebrae 10, 11, and 12. In this scenario, concern should be high for tuberculous osteomyelitis (Pott's disease). In addition to performing a magnetic resonance image of his thoracic and lumbar spines, a chest radiograph should be performed. In addition, an intradermal skin test for tuberculosis using purified protein derivative (PPD) should be placed. Because of the high level of suspicion for tuberculosis, the appropriate local or regional health department should be alerted so the other household members and other potential contacts can also be tested as expeditiously as possible.

## 30.5 Exercises

Please refer to the supplementary information section for answers to these exercises.

1. Of the following, the BEST antibiotic option to treat an uncomplicated joint infection caused by methicillin-susceptible *S. aureus* infection is:
   A. Oxacillin
   B. Vancomycin
   C. Rifampin
   D. Ceftriaxone

2. Of the following, the patient MOST at risk for osteomyelitis with a *Salmonella* species is:
   A. A newborn
   B. An unimmunized 6 years old
   C. An 8 years old with sickle cell disease
   D. A child with indwelling hardware used to stabilize an unstable fracture of the ulna

3. Of the following, the MOST common length of antibiotic therapy for uncomplicated acute hematogenous osteomyelitis is:
   A. 3 weeks or less
   B. 4 weeks
   C. 8 weeks
   D. 52 weeks

4. Of the following, the MOST sensitive and specific imaging test used to diagnose acute osteomyelitis is:
   A. Plain radiograph
   B. Computed tomography
   C. Technetium phosphate radionuclide scan
   D. Magnetic resonance imaging

## Further Reading

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# Candidiasis

**The Laboratory Report States that there are Yeast in the Blood Culture!**

*Ankhi Dutta*




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**Learning Objectives**

- To describe the spectrum of diseases caused by *Candida* species
- To understand the differences between invasive and non-invasive candidiasis
- To identify the clinical features of candidiasis and how they differ by age
- To plan diagnostic strategies to identify candidiasis
- To manage patients with candidiasis with appropriate antifungal agents



## 31.1 Introduction

*Candida* are small thin-walled unicellular yeasts that reproduce by budding. They grow well in standard blood culture media and on sheep blood agar plates. Specialized fungal culture media used for the isolation of molds are not needed. *Candida* form shiny, smooth, creamy-white colonies on sheep blood agar and can sometimes be confused with colonies of staphylococci to the untrained eye. Candida are, round or oval in shape, may demonstrate budding and stain Gram positive on Hematoxylin-Eosin stain. Microscopically, they are easy to distinguish from Gram-positive cocci because the cells are so much larger than bacteria (Fig. 31.1).

There are more than 150 species of *Candida*. Among them, only a few are known to cause diseases in humans, identifying them as medically important yeasts. *Candida* are normal commensals in human, colonizing the skin, gastrointestinal and genitourinary tracts, and upper respiratory tract. All of the medically important species are capable of adhering to exogenous material such as intravascular catheters, bladder catheters, ventriculoperitoneal catheters, and endotracheal tubes explaining their somewhat prominent role in hospital-acquired infections. The host immune response to infection is heavily dependent on neutrophil phagocytosis and killing [1, 2]. The cellular immune response includes the production of opsonizing antibodies that facilitate neutrophil phagocytosis, as well as cytotoxic T-lymphocyte and NK-cell activity [1, 2]. As such, the health of the host's immune system plays a major role in the extent and severity of disease caused by *Candida* species.

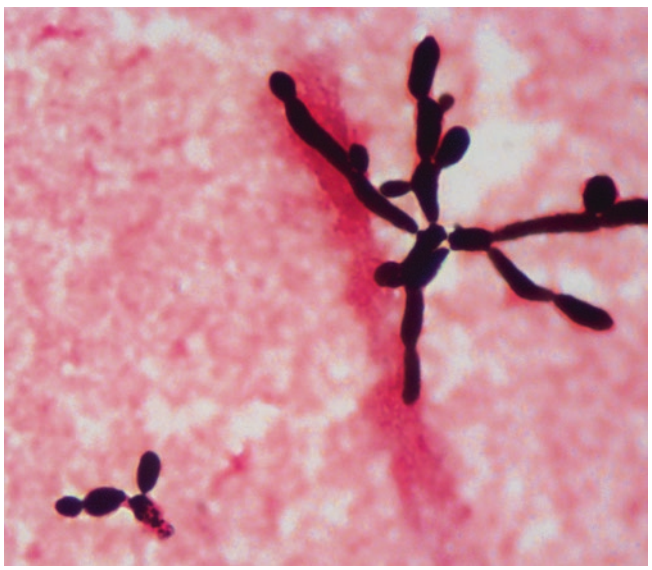

**Fig. 31.1** This Gram stain was performed on a positive blood culture. Note the presence of large Gram-positive (very dark purple, nearly black) ovoid organisms that appear to be budding. The organism was subsequently identified as *Candida albicans*. (Image provided by Dr. Scott Riddell)

**Table 31.1** Treatment options for resistant *Candida* species

| Antifungal susceptibility | Species | Treatment |
|---|---|---|
| Azole resistant | *C. krusei*<br>*C. glabrata* | Echinocandin<br>Amphotericin B |
| Amphotericin B resistant | *C. lusitaniae* | Echinocandin<br>Azole |

Risk factors for the development of candidiasis include the use of broad-spectrum antibiotics, use of oral or inhaled glucocorticoids, treatment with chemotherapy or radiation therapy for underlying malignancy, diabetes mellitus, neutropenia, and primary or acquired defects in cell-mediated immunity. Neonates, especially those born prematurely and those born with a birth weight of less than 1500 g, are also at high risk for developing candidiasis [3–6].

*Candida albicans* accounts for the vast majority of mild to moderate infections in normal hosts and remains the most common species to cause infection in immunocompromised individuals. It accounts for approximately 45% of all invasive candidiasis cases [4]. Other commonly identified non-*albicans* species that cause invasive infection include *C. parapsilosis*, *C. glabrata*, and *C. krusei* [4, 7]. Infections caused by different species of *Candida* are clinically indistinguishable from one another; however, identifying the causative organism to the species level is important because of major differences in antifungal susceptibility patterns. For example, *C. albicans* is nearly always susceptible to azole class medications, but *C. glabrata* and *C. krusei* are not. Similarly, amphotericin B is highly effective against all *Candida* species except for *C. lusitaniae* (Table 31.1).

## 31.2 Noninvasive Candidiasis

### 31.2.1 Oropharyngeal Infection (Thrush)

**Clinical features** - Oral thrush is characterized by creamy-white curd-like patches on the tongue and/or buccal mucosa. The patches can be removed by scraping with a tongue blade typically leaving behind a raw, bleeding, and painful surface. Thrush is common in healthy neonates and young infants; however, it can occur in older children and adults who have been exposed to antibiotics or oral or inhaled steroids or who are immunocompromised [8].

**Diagnosis** - Oral thrush is diagnosed by it clinical appearance. Microbiological confirmation is rarely needed. If microbiological confirmation is necessary, a potassium hydroxide wet mount preparation, Gram stain, or calcofluor white smear can be done to show the yeast forms. Culture of the lesions is not indicated unless it is refractory to treatment or recurrent or the diagnosis is doubtful [8, 9]. Cultures do not differentiate between colonization and infection.

**Treatment** - Oral candidiasis can be treated topically with nystatin suspension or clotrimazole. In addition to treating with topical antifungal agents, advice regarding the prevention of reinfection is important, particularly for young infants. Pacifiers and bottle nipples should be boiled after each use. Lactating mothers should be evaluated for candidiasis of the nipples and treated accordingly. Treatment should be continued for 2–3 days after complete resolution of symptoms to avoid immediate recurrence. Oral candidiasis typically resolves within 2 weeks of initiating therapy. If there is persistent candidiasis beyond the 2-week period, infection due to resistant *Candida* species and/or an alternative diagnosis should be considered [8].

Oral fluconazole is the second line of therapy if nystatin therapy fails. Failure of fluconazole therapy warrants culture of the lesion to rule out the presence of an azole-resistant *Candida* species (*C. krusei* or *C. glabrata*). An evaluation for immunodeficiency should also be considered for patients who present with recurrent or persistent oral candidiasis.

Fluconazole is more effective than nystatin suspension for the treatment of oral candidiasis in immunosuppressed patients. If fluconazole-resistant strains are suspected, other therapeutic options include oral itraconazole, oral posaconazole, intravenous amphotericin B, or intravenous echinocandin.

### 31.2.2 Esophageal Candidiasis

Esophageal candidiasis can occur with or without oral thrush. It has been reported in immunocompetent hosts, although it is much more commonly seen in immunocompromised individuals. The most common symptoms of esophageal candidiasis include odynophagia, substernal chest pain, and a feeling of obstruction when swallowing [8]. Nausea and vomiting can occur. In the immunocompromised host, *Candida* esophagitis can coinfect along other causes of esophagitis including herpes simplex virus and cytomegalovirus [8, 9].

**Diagnosis** - *Candida* esophagitis is diagnosed by endoscopic visualization and biopsy. Characteristic white plaques are seen during the procedure. Scrapings and biopsy material show budding yeast [8, 9].

**Treatment** - Fluconazole is the first-line treatment for esophageal candidiasis. In refractory cases, other antifungal medications such as amphotericin B or an echinocandin may be necessary.

### 31.2.3 Chronic Mucocutaneous Candidiasis

Chronic mucocutaneous candidiasis is characterized by recurrent and/or refractory candida infections of the skin, mucus membranes, nails, and hair. It can be associated with autosomal recessive polyglandular autoimmune syndrome type I (hypoparathyroidism, hypothyroidism, and adrenal insufficiency). The disease is caused, at least in part, by failure of an effective T-lymphocyte response to *Candida* antigens. The immunodeficiency appears restricted to responses to *Candida*. Invasive infection does not occur. Chronic, suppressive antifungal therapy is required [8].

### 31.2.4 Candidal Vulvovaginitis

Candidal vulvovaginitis can occur at any age. Predisposing factors include prior antibiotic or steroid use, oral contraceptive use, estrogen therapy, diabetes mellitus and immunosuppression [8]. The most common clinical features are vaginal discharge and itching. Other clinical manifestations may include dysuria, vaginal irritation, and dyspareunia [8]. Clinical examination reveals vulvar erythema and edema associated with a thick curd-like or watery vaginal discharge.

**Diagnosis** - The diagnosis of vulvovaginal candidiasis is usually made based on the characteristic clinical presentation. If confirmation is needed, a KOH wet mount preparation of vaginal secretions can be done to demonstrate the presence of budding yeast. Vaginal cultures are indicated only in treatment failures because *Candida* normally colonizes the female genitourinary tract. Again, cultures do not differentiate between colonization and infection. Good clinical judgment does.

**Treatment** - Vulvovaginitis can be treated topically or orally with antifungal agents. Topical options include intravaginal clotrimazole, miconazole, or terconazole. Oral fluconazole can also be used.

### 31.2.5 Candida Diaper Dermatitis (Fig. 31.2)

*Candida* is a common cause of diaper dermatitis in infants. It involves the perianal area and the perineum with "satellite" lesions spreading over the warm, moist areas covered by the diaper. The diagnosis is made clinically. Physical examination

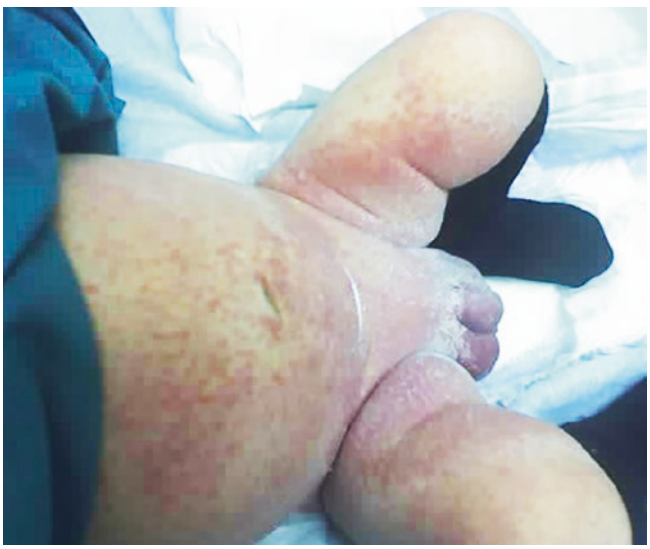

**Fig. 31.2** Shown is a 4-month-old boy with candida diaper dermatitis. Note the underlying erythema and the extensive numbers of satellite lesions. The spread beyond the usual diaper area, as shown here, is atypical. (Image provided by Dr. Joseph Domachowske)

reveals an erythematous rash with small pruritic satellite lesions confined to the diaper area [8]. In more advanced cases, the inflammatory component of the infection can give the involved skin an impressively "angry" erythematous appearance.

**Treatment** - Diaper dermatitis can be treated topically with nystatin cream. Oral fluconazole is required for refractory cases. Allowing the infant to go for prolonged periods without a diaper if feasible, might have a soothing drying effect and can speed recovery.

### 31.2.6 Other Miscellaneous Noninvasive Candida Infections

Other noninvasive candida infections include balanitis, intertrigo, and paronychia, all of which are diagnosed on clinical grounds. Localized lesions can be treated with topical antifungal agents. Refractory cases can be treated with oral fluconazole.

## 31.3 Invasive Candidiasis

Invasive candidiasis is used to describe infections that are associated with candidemia, with or without metastatic seeding of other sites. It is a major cause of morbidity and mortality in hospitalized patients and accounts for between 8 and 10% of all bloodstream infections reported in the United States [10].

**Risk factors** - Underlying medical conditions and their associated risk factors increase the risk of candidemia. One of the most impactful predisposing factor is the presence of an indwelling vascular catheter that allows a portal of entry for the yeast (Fig. 31.3). As additional risk factors are added, the likelihood for *Candida* to cause invasive infection increases. For example, a patient with acute leukemia receives intravenous chemotherapy via a central venous catheter. The treatment regimen also includes prednisone, a glucocorticoid. Two weeks later, the patient experiences an episode of high fever, and because of chemotherapy-induced neutropenia, he is hospitalized and treated with broad-spectrum antibiotics. He is now profoundly immunosuppressed. Broad-spectrum antibiotics allow for yeast overgrowth on areas where he is colonized, and he has easy access of *Candida* to the bloodstream from chemotherapy-associated mucositis or via his indwelling catheter.

Other associated risk factors for the development of invasive candidiasis include recent surgery (especially on the gastrointestinal tract), receipt of total parenteral nutrition, short-gut syndrome, solid-organ and hematopoietic stem cell transplants, and extreme prematurity [4, 6, 11, 12].

Among the pediatric population, neonates form a unique group and differ from older children and adults with respect to incidence and outcome of invasive candidiasis.

### 31.3.1 Neonatal Invasive Candidiasis

Invasive candidiasis and candidemia are leading causes of mortality among extremely low birth weight (ELBW) infants (<1000 g) in the neonatal intensive care units [3] . Mortality from Candida infections is higher among ELBW babies than older children. Infection is also associated with poor neurodevelopmental outcomes [3]. The immature skin structure and relative immunodeficiency related to reduced T cells and decreased neutrophil function predispose premature neonates to invasive disease. In addition to the traditional risk factors associated with candidiasis, colonization of the skin, gastrointestinal tract, and respiratory tract has been found to be an important risk factor for candidiasis in ELBW neonates [13].

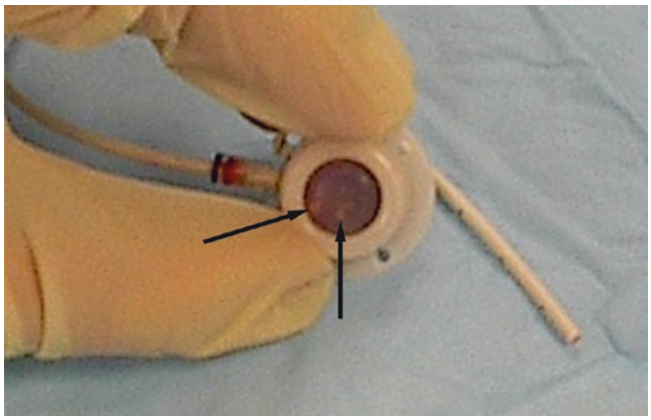

**Fig. 31.3** This central venous catheter was removed from a patient with persistent candidemia. The circular reservoir of this type of device is covered with a translucent diaphragm. At the time of surgical placement, the catheter is inserted into a central vein, and the reservoir portion of the device is implanted just under the skin. When vascular access is needed, a needle is inserted through the skin, through the diaphragm, and into the reservoir. This patient developed fevers. Blood cultures collected daily through the catheter grew *Candida parapsilosis* each time for 4 days despite treatment with amphotericin B, so the device was removed. Note the colonies of yeast that are just visible behind the translucent diaphragm of the reservoir (*arrows*). (Image provided by Dr. Joseph Domachowske)

***Candida* species distribution in neonatal infections** - *C. albicans* is the most common, and *C. parapsilosis* is the second most common species to cause neonatal candidiasis. *C. tropicalis*, *C. lusitaniae*, *C. glabrata*, and *C. krusei* account for most of the remaining cases. The emerging pathogen, *C. auris*, has already been reported as a cause of neonatal invasive infection and has been predicted to become more problematic. In recent studies, the incidence of candidemia in neonatal intensive care units has shown decreasing trends, most likely owing to improved infection control practices and the use of fluconazole prophylaxis in ELBW infants [7]. Non-*albicans* species account for most late-onset candida infections and are most likely acquired from the hospital environment.

**Sites of infections** - Candidemia is the most common manifestation of neonatal invasive candidiasis. Metastatic infection secondary to hematogenous seeding of other sites is common. Urinary tract infection, meningitis, endocarditis, endophthalmitis, osteomyelitis, septic arthritis, and abscesses of the kidneys, liver, and spleen have all been described. Disseminated disease involving multiple different sites is not uncommon.

**Clinical manifestations** - The signs and symptoms of neonatal candidemia are indistinguishable from bacterial sepsis. Neonates can present with septic shock, temperature dysregulation (fever or hypothermia), respiratory distress, lethargy, irritability, or skin lesions. Congenital candidiasis is a distinct entity that occurs following in utero

exposure to *Candida*. These infants present with an erythematous macular or papular rash on the first day of life (Fig. 31.4). The papules progress to form vesicles, pustules, or bullae. Infection is usually confined to the skin surface. Dissemination is rarely seen, but is a risk for premature infants.

**Diagnosis** - Isolation of *Candida* species from a normally sterile site such as the blood, cerebrospinal fluid, urine, or bone marrow establishes a diagnosis of invasive candidiasis [9]. If a central venous catheter is present, blood cultures should be collected from both the catheter and from a peripheral vein. All neonates with documented candidemia should undergo a careful evaluation for the presence of metastatic infection. Blood, urine, and cerebrospinal fluid cultures should be collected. A dilated eye examination and echocardiogram should be performed. Imaging of the kidneys, liver, and spleen should also be completed [9]. Ultrasonography is appropriate as the first-line imaging modality in neonates. If meningitis is suspected, neuroimaging is necessary.

**Treatment** - Available systemic antifungal medications are summarized in Table 31.2.

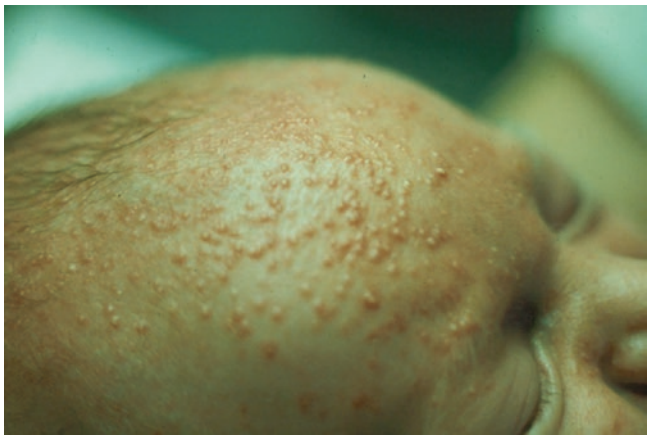

**Fig. 31.4** The rash shown on this newborn's face and scalp is typical for congenital candidiasis. It was noted at the time of birth and was also present on his trunk and extremities. (Image provided by Dr. David Clark)

**Table 31.2** Available antifungal medications

| Class of drug | Medications | Mechanism of action | Indications | Major side effects |
|---|---|---|---|---|
| Polyenes | Amphotericin B (AmB) deoxycholate<br>Lipid formulations of AmB | Bind to ergosterol and promote osmotic lysis by creating transmembrane channels | 1. First-line therapy for NC<br>2. Lipid formulations preferred for neutropenic patients with candidemia<br>3. First-line therapy for DC<br>4. First-line therapy for endocarditis<br>5. First-line therapy for CNS candidiasis<br>6. Osteoarticular infections | 1. Nephrotoxicity<br>2. Electrolyte imbalance especially hypokalemia, hypomagnesemia, hypocalcemia<br>3. Infusion reactions (chills, rigors, fevers) |
| Echinocandins | Caspofungin<br>Micafungin<br>Anidulafungin | Interfere with cell wall biosynthesis by noncompetitive inhibition of beta-1,3 glucan production | 1. Non-neutropenic patients with candidemia<br>2. Fluconazole-resistant strains<br>3. Neutropenic patients with candidemia<br>4. Alternative therapy for DC<br>5. Alternative for endocarditis<br>6. Alternative for osteoarticular infections | Hepatic dysfunction |
| Systemic azoles | Fluconazole | Inhibit fungal cytochrome P-450 (lanosterol alpha demethylase) which blocks demethylation of the C-14 of lanosterol leading to substitution of the methylated sterols and depletion of ergosterol | 1. Refractory localized candidiasis<br>2. Step-down therapy for candidemia in neutropenic and non-neutropenic patients<br>3. NC as a step-down therapy<br>4. Osteoarticular infections<br>5. Esophageal candidiasis | Hepatic dysfunction<br>Drug interactions due to CYP enzyme system |
| Newer systemic triazoles | Voriconazole<br>Posaconazole | | Second-line therapy in neutropenic patients as step-down therapy, rarely used for candida infections | Hepatic dysfunction<br>Drug interactions with CYP system |
| Topical azoles | Miconazole<br>Clotrimazole<br>Ketoconazole | | 1. Localized candidiasis (vulvovaginitis, balanitis, intertrigo, diaper dermatitis)<br>2. Congenital candidiasis | |
| | Nystatin | | 1. Oral candidiasis<br>2. Candida diaper dermatitis<br>3. Congenital candidiasis | |

*NC* neonatal candidiasis, *DC* disseminated candidiasis, *CNS* central nervous system

The drug of choice for the treatment of invasive neonatal candidiasis, including meningitis, is amphotericin B deoxycholate [14]. Neonatal CNS candidiasis is treated for at least 21 days. Treatment should continue until all signs and symptoms of candidiasis, cerebrospinal fluid and imaging abnormalities have resolved. [9, 14].

For non-CNS candidiasis, fluconazole could be used if the *Candida* species is known and the *Candida* species is susceptible to fluconazole. The duration of therapy for uncomplicated candidiasis is 14 days, provided there is documented clearance of *Candida* and symptoms have resolved clinically [9, 14].

The data on echinocandins and newer azoles are insufficient to make general recommendations for use in neonates, but are used clinically when necessary with advice from expert consultants.

All central venous catheters should be removed promptly in the setting of candidemia.



### 31.3.2 Invasive Candidiasis Beyond the Neonatal Period

**_Candida_ species distribution of invasive candidiasis beyond the neonatal period** - *C. albicans* predominates, followed by *C. parapsilosis*, *C. glabrata*, *C. tropicalis*, and *C. krusei*. Non-*albicans Candida* have been reported more commonly in oncology patients and those with gastrointestinal disorders especially among children with short-gut syndrome [4, 6]. *C. rugosa* has been associated with burns. *C. auris* has also emerged as a multidrug-resistant, highly virulent pathogen.

**Sites** - The most common organs involved include the lungs and the liver [4]. The risk for disseminated candidiasis increases with persistent candidemia (3 or more consecutive days of positive blood cultures) especially in patients who are immunosuppressed and who have a central venous catheter in place [12]. Dissemination can lead to metastatic chorioretinitis, endophthalmitis, endocarditis, or involvement of other solid organs including the liver, kidney, or spleen.

**Diagnosis** - Isolation of *Candida* species from a normally sterile site (blood, cerebrospinal fluid, bone marrow) or demonstration of the organism in tissue specimens. A positive serum antigen test for the presence of (1,3)-beta-D-glucan, a component of the fungal cell wall, supports but does not confirm the presence of invasive candidiasis.

A comprehensive diagnostic evaluation for the presence of metastatic foci should be considered for all patients with candidemia. Computed tomography (CT) is helpful to evaluate the liver, spleen, and kidneys. An echocardiogram should be performed to rule out involvement of the heart, and an ophthalmological examination is necessary to evaluate potential spread to the eyes [14].

**Treatment** - All central venous catheters should be promptly removed in the setting of candidemia. Systemic antifungal drugs and their mechanism of actions are shown in Table 31.2.

In non-neutropenic patients, fluconazole or an echinocandin is the drug of choice [14]. Amphotericin B can be used as an alternative. Uncomplicated candidemia, without evidence of dissemination, is treated for 14 days, once there is documented clearance of *Candida* from the blood [14].

In neutropenic patients, lipid formulations of amphotericin B or an echinocandin is recommended [14]. Candidemia, without dissemination, is treated for 14 days once there is documented clearance of the organism from the bloodstream [14]. Neutropenic patients with evidence of disseminated candidiasis may require treatment for weeks to months.

## 31.4 Conclusion

Candidiasis is a significant cause of morbidity and mortality. Localized infections are common in otherwise healthy individuals and can generally be treated with available topical therapies. Invasive infections typically occur in patients who are immunosuppressed or have other identifiable risk factors. Most noninvasive candida infections can be diagnosed based on typical clinical findings. The diagnosis of invasive candidiasis requires microbiological and radiologic confirmation. Prompt identification of and treatment for candidemia are essential to prevent disseminated disease.

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# Tick and Mosquito Borne Diseases and Tropical Infections of Global Importance

Contents

# Lyme Disease

**Bulls Eye Rash or**
**Fever, Headache, Stiff Neck or**
**Facial Palsy or**
**A Swollen Painful Knee**

*Nicholas J. Bennett*




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**Learning Objectives**

- Know the etiologic agent of Lyme disease and how the infection is acquired.
- Describe the classic clinical presentations of Lyme disease.
- Accurately interpret the results of Lyme diagnostic testing in the appropriate clinical context.
- Understand the advantages and limitations of various treatment approaches for Lyme disease.
- Be aware of controversies surrounding Lyme disease and the risks associated with its incorrect management.

## 32.1 Introduction to the Problem

Lyme disease is a condition that is at once simple and yet complex. Much has been laid at the feet of Lyme disease that is unwarranted. To establish an accurate diagnosis and to plan an appropriate treatment regimen for a patient with Lyme disease, providers need to have a clear understanding of its pathogenesis. In recent years Lyme disease cases have been reported with increasing frequency across the United States in part and observation that has led to considerable public anxiety regarding an "epidemic." A major cause for this increase in reported cases is an overall better recognition of the spectrum of illness caused by *Borrelia burgdorferi.* Although the diagnosis and treatment of Lyme disease should be relatively straightforward given the availability of clinical practice guidelines that clearly outline recommended serologic testing guidelines and options for the 14- to 28-day courses of antibiotics, several issue care arises to complicate the management of the disease. First, the tick species that transmit *B. burgdorferi* are also known to transmit other pathogens including the agents that cause anaplasmosis and babesiosis, so the possible presence of a coinfection should be considered. Next, infection with *B. burgdorferi* does not confer long-term protective immunity from reinfection, yet the *B. burgdorferi*-specific IgG antibodies that were produced in response to the infection, and used to establish the diagnosis, continue to be detectable for many years. Since serologic testing is necessary for diagnosis, the persistence of *B. burgdorferi*-specific IgG antibodies complicates the ability to interpret serologic test results when the test is repeated because of the suspicion that the patient has been reinfected. *B. burgdorferi* is highly susceptible to antibiotics. Patients who are diagnosed and treated for Lyme disease with an appropriate antibiotic regimen are cured from their infection. Some patients go on to experience persistent, typically vague, symptoms such as fatigue, headache, and myalgia following appropriate treatment. Prolonged fatigue, often in association with other symptoms, is known to occur following a variety of acute infections. For example, prolonged, profound fatigue can persist for months following acute mononucleosis. Similarly, some adolescents and adults experience prolonged fatigue following acute parvovirus B19 infection. The precise mechanism of or underlying risk factors for developing post-infection prolonged symptoms of "unwellness" are unknown. Patients who continue to experience such symptoms after treatment for Lyme disease should undergo a full assessment of those symptoms to be sure that the initial Lyme diagnosis was accurate and that their antibiotic treatment regimen (specific medication, dose, dosing interval, and length of therapy) was appropriate. Careful attention should be paid to assessing whether a second illness may have also been present at the same time as the initial Lyme diagnosis and that a new illness has not developed since completion of the antibiotic regimen. Assuming the initial Lyme diagnosis was accurate, and the treatment regimen appropriate, attention should be given to carefully explain to the patient that while the persistence of some of their symptoms is yet unexplained, their infection has been treated. Additional antibiotics are both unnecessary and potentially harmful. Ongoing medically unexplained symptoms may require consultation with other medical specialists. Finally, some patients with medically unexplained symptoms present for care convinced that their problems are indeed related to Lyme disease despite one or more negative serologic test results. Engaging such patients to consider alternative causes for their symptom complex can be particularly challenging. Some seek out providers who either recommend or agree to prescribe complex and prolonged antibiotic courses rather than those who will work with them to identify and/or treat the valid cause(s) of their complaints.

## 32.2 Epidemiology

Lyme disease was first described in the 1970s among children living in Lyme, Connecticut, USA, initially as a cause of persistent idiopathic joint inflammation that shared features with juvenile rheumatoid arthritis [1–4]. It became apparent that an infectious agent was the likely cause of the illness based on the clinical progression of the symptoms prior to the development of chronic arthritis.

Lyme disease is endemic to specific geographic areas of the United States because of the geographic distribution of its tick vectors *Ixodes scapularis* along the east coast, and *I. pacificus* on the west coast, and the distribution of deer and the white-footed mouse, the natural mammalian life cycle hosts of *B. burgdorferi* [5, 6]. Fourteen (28%) of the 50 states account for 96% of Lyme disease cases reported to the Centers for Disease Control and Prevention (CDC) (Fig. 32.1). Based on reviews of laboratory testing data and health insurance claims reports, the Lyme disease burden in the United States is estimated at 300,000 new cases annually, although only one tenth as many are officially reported to the CDC [7–9]. Difficulties in interpreting such estimates include reliance on the accuracy of insurance claims and counting positive test results as individual cases. Every positive test result is unlikely to represent a discrete case of Lyme disease since some represent repeat testing of the same patients more than

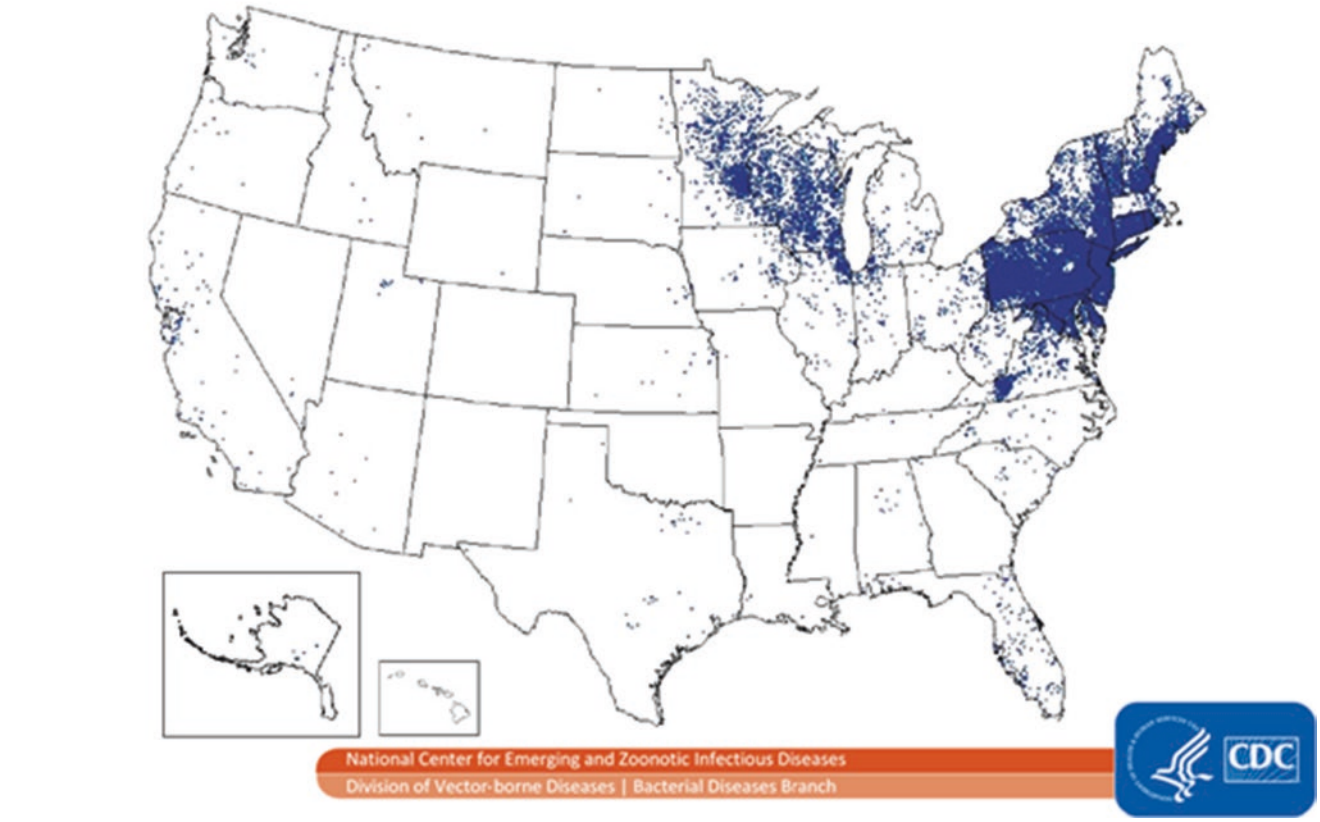


**Fig. 32.1** Geographic location of reported cases of Lyme disease, 2016 data. (Courtesy of CDC)

once during that year. Since serologic testing relies on the detection of multiple *B. burgdorferi*-specific IgG antibodies, and those antibodies are detectable in the patient blood for months to years after infection, all patients diagnosed with Lyme disease by Western blotting will continue to test positive by that technique for prolonged period of time. Results of repeat testing do not offer any assessment of the patient's response to therapy since effective antibiotic treatment has no effect on the Western blot IgG banding pattern. As such, repeat serologic testing after the diagnosis of Lyme disease has been confirmed will not offer any additional useful information. Despite the limitations of the methods used to estimate the disease burden in the United States, it is clear that Lyme disease continues to cause substantial morbidity, particularly in the geographic areas where it has remained endemic.

The seasonal life cycles of the tick vectors for Lyme disease explain why new human infections are seen most commonly during the spring and fall. The majority of Lyme disease cases that are diagnosed during the winter months present with signs and symptoms of disseminated or late disease rather than the localized rash of ECM. The *Ixodes* ticks that transmit the infection mature during a 2-year period, passing through three distinct stages of growth. At each stage, a blood meal is required for the arthropod to further mature. The tiny six-legged larvae hatch during the late spring and summertime but remain uninfected until their blood meal, which is typically obtained from a small rodents or a bird. The eight-legged nymphal stage matures during the springtime of the following year, tending to feed on larger animals, such as deer and humans. It is during this developmental stage where an infected nymph first has the ability to transmit Lyme disease to humans. During the fall months of the same year, eight-legged nymphs that have successfully obtained a blood meal mature into adult ticks. Adult female ticks obtain another blood meal prior to laying eggs. The eggs hatch during the following spring and summer beginning a new cycle of reproduction (Fig. 32.2).

To obtain a blood meal, a tick first needs to attach itself to the skin of the mammalian host. Attachment, by itself, is not sufficient for transmission of *B. burgdorferi* from an infected tick to its host. The bacteria reside in the midgut of the infected tick. After the tick attaches to the skin of the host to begin feeding, the midgut spirochetes undergo a series of adaptive

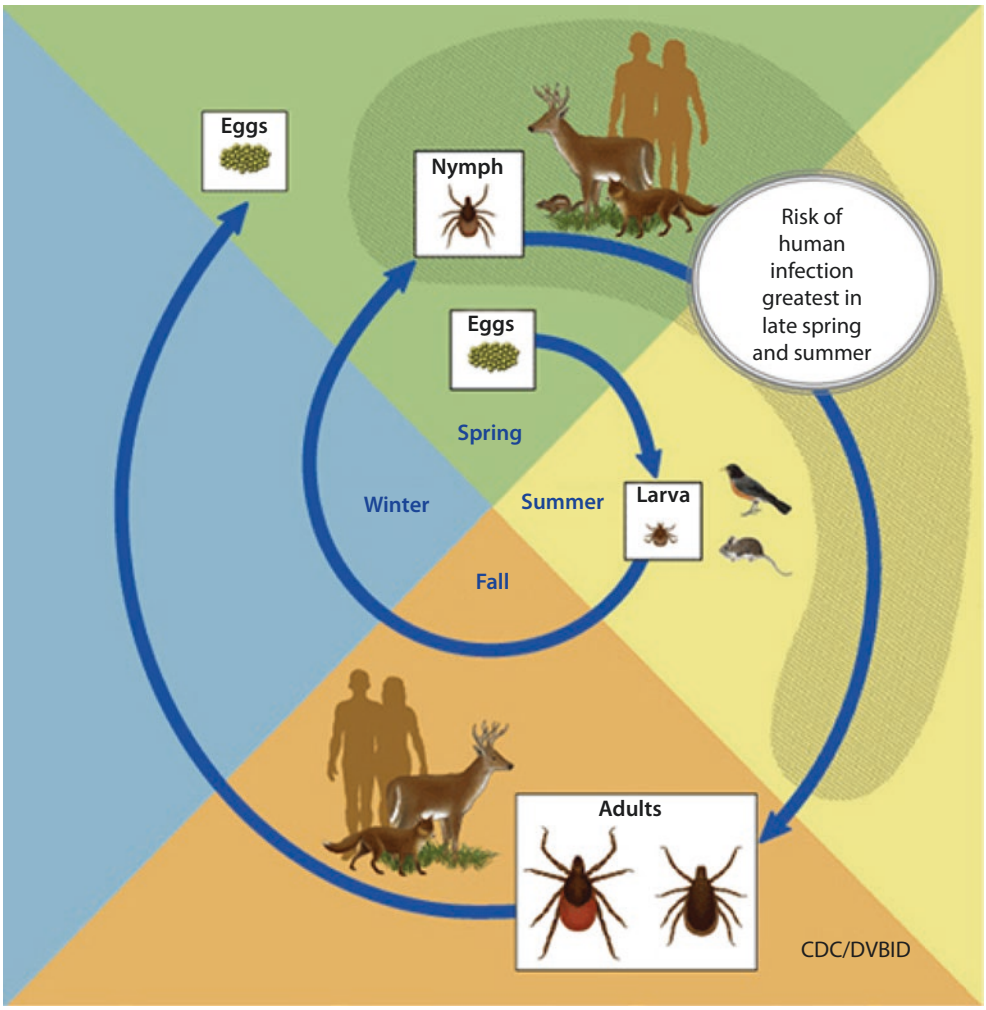


**Fig. 32.2** Life cycle of the *Ixodes scapularis* (black-legged tick). (Courtesy of CDC)



changes that facilitate transmission to and survival within the mammalian host [10–17]. The adaptive changes needed to ease transmission of the infection occur over a 48-h period of time if the tick remains attached. If a tick is removed prior to being fully engorged, the transmission of Lyme disease can be effectively interrupted [18]. Uncommonly, transmission may occur during a more abbreviated time frame [19].

Some patients with Lyme disease report removing only unengorged ticks from their skin, while many others report that they have never removed one. In both circumstances, it is highly likely that an infected tick remained attached, became fully engorged, and transmitted the infection to the patient without being noticed. Any patient who has removed *Ixodes* ticks from their skin is at risk for developing Lyme disease whether the ones they removed were thought to be engorged or not. Transmission only requires that a single infected tick escapes the patient's attention long enough to become engorged. Family pets or other members of a household have the potential to carry ticks into a house on their clothing. As such, it's possible for homebound individuals, young infants, or household members who rarely or never spend time in grassy or wooded areas outdoors to find a tick on their body or to develop Lyme disease without ever having noticed the engorged tick that took its blood meal from them after inadvertently being brought inside the house. A thorough medical history helps in assessing a patient's risk for Lyme disease. The discussion should include details about where the patient lives and where they have traveled; tick prevention strategies they use for their family pets; whether other members of their household have experienced a tick-borne infection, including Lyme disease; and whether they have ever removed a tick from their body or the body of another member of the household. Specific information regarding occupational and recreational outdoor activities should also be documented. Taken together, information collected during the social history allows for an excellent assessment of a patient's risk for having contracted Lyme disease.

## 32.3 Clinical Presentations

Lyme disease can be classified into three distinct stages, each associated with distinct clinical syndromes: early localized disease, early disseminated disease, and late disease. Each stage carries associated implications related to diagnosis, treatment, and long-term prognosis.

Early localized infection is a clinical diagnosis, based on the presence of a single, typical red bull's-eye lesion on the

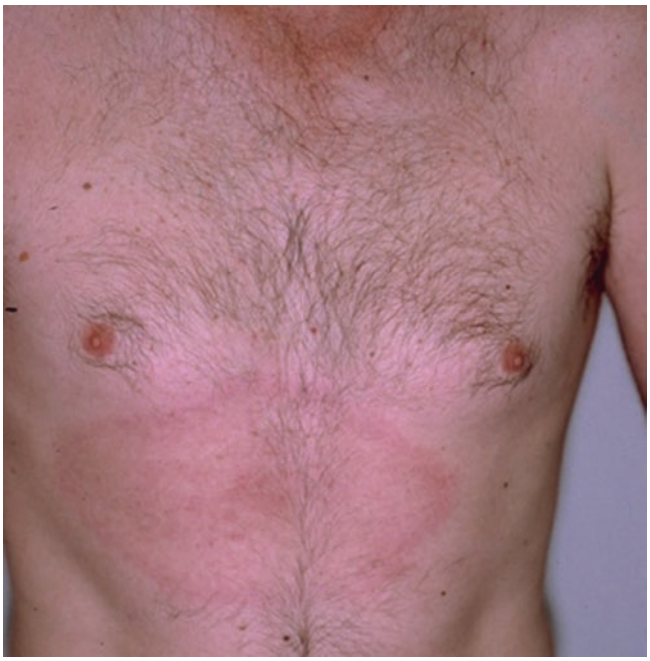

**Fig. 32.3** This man has a large, red bull's-eye lesion on his trunk consistent with erythema chronicum migrans, the rash typically seen during early, localized Lyme infection. (Image provided by Dr. Henry M. Feder, Jr)

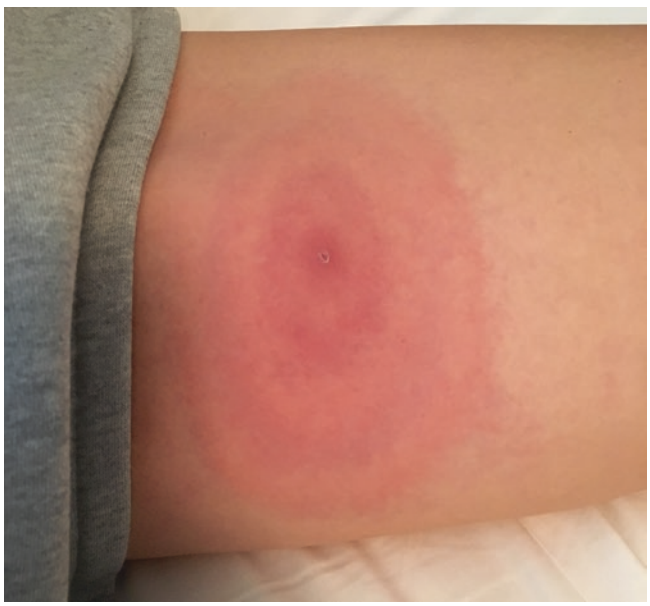

**Fig. 32.4** This woman has a classic erythema chronicum migrans rash on her leg. (Image provided by Dr. William Prince)

skin referred to as erythema chronicum migrans (ECM) (Figs. 32.3 and 32.4). Some patients also experience headache, fatigue, and/or myalgias. The ECM rash consists of a central area of erythema, which may blister or scab, associated with an expanding ring (or rings) of erythema that gradually fades along the inner aspect as the rash spreads, thus giving the appearance of a bull's-eye. ECM appears at the site where the infected tick was once attached but several days to 2 weeks later. The development of local erythema while the tick is attached, and/or shortly after it is removed, does not indicate early localized Lyme disease but is instead a fairly common, self-limiting local inflammatory response to the tick bite itself. The diagnosis ECM is made clinically based on the classic features of the rash. Serologic testing is not recommended during early localized Lyme disease because the production of *B. burgdorferi*-specific IgM antibodies requires a minimum of 2 weeks, and IgG antibody production requires 4 weeks. Skin biopsies and cultures of the ECM lesions were performed in the past but are no longer considered necessary. Patients who present with a skin rash consistent with ECM who live in or have traveled to Lyme endemic areas should be treated for early localized Lyme disease. The inclination to request serologic testing to "confirm" the clinical diagnosis is discouraged [▶ Call Out Box 32.2].

Lyme disease is not endemic across the Southern United States, but infections caused by *Borrelia lonestari*, a bacterium transmitted by the lone star tick *Amblyomma americanum*, are seen regularly among patients who live or travel to Texas and neighboring states to the east. Patients who become infected with *Borrelia lonestari* typically develop a rash along with mild to moderate systemic symptoms including fever, fatigue, and myalgia. The rash seen with what is now referred to as "southern tick-associated rash illness" or "STARI" is clinically indistinguishable from ECM.

When early localized Lyme disease goes unrecognized, any associated symptoms resolve. Without antibiotic treatment, the bacteria, once localized to the inoculation site where the infected tick was attached, disseminate. Early disseminated Lyme disease typically occurs 1–4 weeks after the initial infection. During dissemination, patients experience

**Call Out Box 32.1**
Testing for Lyme disease requires a two-tier serological approach where positive or equivocal enzyme immunoassay screening tests for antibodies to *B. burgdorferi* are referred automatically for confirmation by Western blot. IgM Western blots that show the presence of at least two out of three antibody bands and IgG Western blots that show the presence of at least five out of ten antibody bands are considered positive results. The positive laboratory result should also be interpreted in the context of the patient's current complaints.

**Call Out Box 32.2**
A clinical diagnosis of early localized Lyme disease should be made in patients who present with the rash of erythema chronicum migrans. Performing Lyme testing on patients with erythema chronicum migrans is both unnecessary and strongly discouraged since the rash occurs within the first 2 weeks of the infection, and testing relies on serologic responses that require more than 2 weeks to be detected. Antibiotic treatment of erythema chronicum migrans cures the infection thereby preventing the emergence of later stages of Lyme disease and their complications.

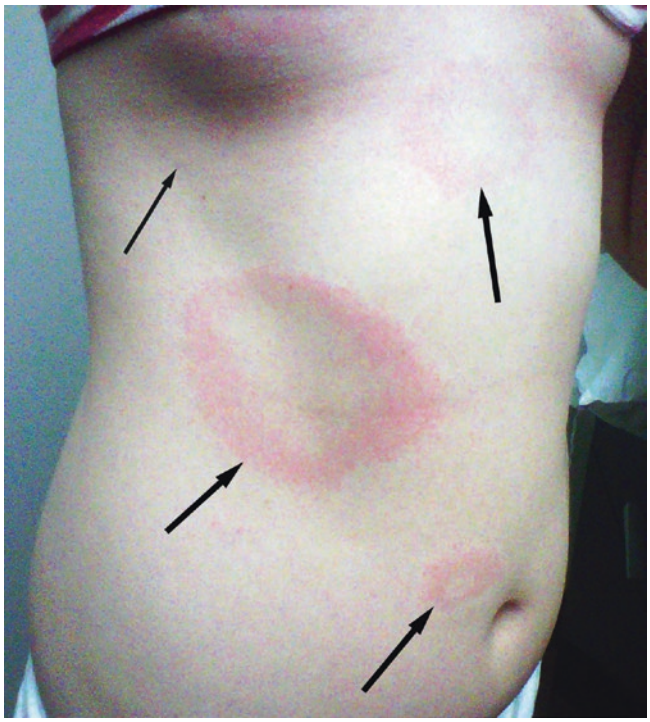

**Fig. 32.5** The presence of multiple erythema chronicum migrans lesions on the skin, as seen here (arrows), represents one of classic clinical presentations for early disseminated Lyme disease. (Image provided by Dr. Joseph Domachowske)

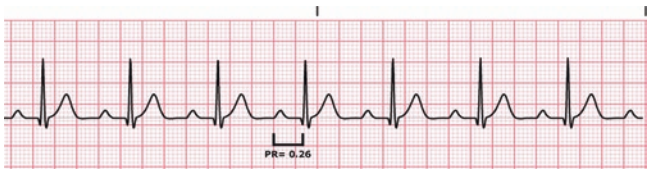


**Fig. 32.6** Shown is an electrocardiogram rhythm strip from an adult patient with Lyme carditis, manifesting as 1st degree heart block. The PR interval shown is measured at 0.26 s. A PR interval greater than 0.20 s meets criteria for 1st degree heart block. (Image provided by Dr. Joseph Domachowske)

systemic symptoms including fatigue, headache, and myalgia. Fever is also common. Specific signs and symptoms most typically involve the skin, the heart, and the nervous system. Even in the absence of any other symptoms, the presence of two or more discrete ECM lesions on the skin indicates that the infection has disseminated (Fig. 32.5). Carditis is another classic manifestation early disseminated Lyme disease. Symptomatic patients may experience episodes of syncope or near-syncope or may report heart palpitations related to cardiac dysrhythmias associated with second or third-degree heart block. Asymptomatic carditis is the more common finding, typically being diagnosed when a patient with suspected disseminated Lyme disease undergoes a screening electrocardiogram that reveals the presence of first-degree heart block (Fig. 32.6). Since an electrocardiogram is not performed on all patients who are diagnosed with early disseminated Lyme disease, it's possible that first-degree heart block is a more common complication than otherwise appreciated. Rare, but well-documented deaths have been reported in patients with Lyme carditis, presumably as a result of a fatal dysrhythmia [20–22].

Neurologic manifestations of early disseminated Lyme disease may involve the central and/or peripheral nervous systems. The two most commonly seen central nervous system manifestations are aseptic meningitis and cranial nerve palsy. Lyme meningitis is an indolent form of meningitis referred to as "aseptic" because, while patients have the classic meningitis triad of fever, headache, and stiff neck, they appear only mildly or moderately ill. When the cerebrospinal fluid is evaluated, a mononuclear cell pleocytosis is seen along with a normal glucose concentration and an elevated total protein concentration. In contrast, patients with bacterial meningitis caused by suppurative pathogens such as *Streptococcus pneumoniae* present with the classic triad of fever, headache, and stiff neck, but they appear to be severely ill or septic. When their cerebrospinal fluid is evaluated, a polymorphonuclear cell pleocytosis is seen along with a depressed, even undetectable glucose concentrations and an elevated total protein concentration. Such patients are said to have "bacterial meningitis," "meningitis with sepsis," or simply "meningitis." The term "septic meningitis," while appropriate and logical, is not used. Since Lyme meningitis is caused by a bacterium, *B. burgdorferi*, technically speaking, it is a form of "bacterial meningitis"; however, to avoid confusion or miscommunication, it's best to avoid that term in favor of "Lyme meningitis." Overall, the clinical picture combined with the results of cerebrospinal fluid testing allows for a straightforward assessment of whether a given patient has "aseptic meningitis," as occurs in Lyme disease and many viral infections, or "bacterial meningitis," as occurs with *S. pneumoniae* and other suppurative bacterial pathogens.

The second group of central nervous system complications that are commonly seen as manifestations of early disseminated Lyme disease are cranial nerve (CN) palsies. Unilateral CN VII palsy (also called Bell's palsy or facial nerve palsy) is, by far, the most common and most classic CN palsy seen as a complication of Lyme disease (Fig. 32.7). In theory, any of the CNs with effector function can be affected. While rare, bilateral involvement of paired nerves has been described for CNs IV, VI, and VII. Lyme encephalitis is a rare but serious central nervous system complication of Lyme disease. The diagnosis should be considered in any patient who presents with encephalitis or meningoencephalitis of unclear etiology. Peripheral neuropathy is much less common than isolated CN palsy as a clinical finding of Lyme disease in the United States, although neuroradiculitis does occur regularly as a feature of Lyme disease in Europe.

A small number of patients previously diagnosed and treated for Lyme disease experience persistent and prolonged neurologic and/or neurocognitive symptoms such as difficulty with memory or concentration, fatigue, and recurrent headaches. Repeated attempts to identify individuals with an ongoing, chronic infection with *B. burgdorferi* as a possible explanation for these problems have not yet been successful.

**Fig. 32.7** Left-sided cranial nerve VII palsy in a woman with early disseminated Lyme disease. Note her facial asymmetry when asked to smile. Her left eye remains fully open, and her lips and mouth remain in neutral position on the left side. (Image provided by Dr. Henry M. Feder, Jr)

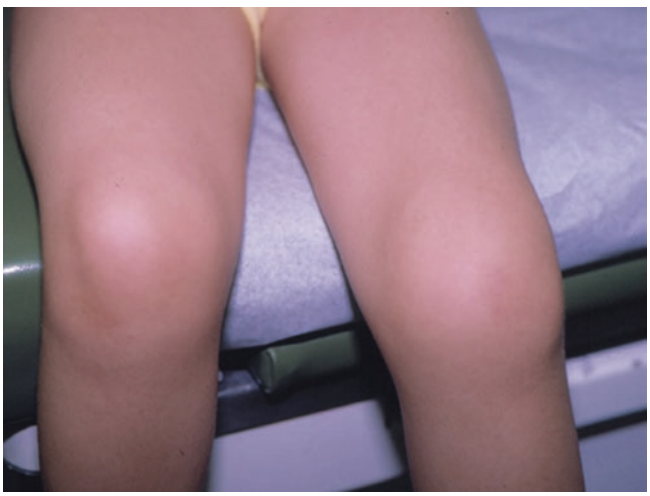

**Fig. 32.8** Left knee effusion in a child with Lyme arthritis. (Image provided by Dr. Henry M. Feder, Jr)

Since "chronic Lyme infection" does not occur, the diagnosis should be rejected as an explanation for a patient's medically unexplained symptoms. Once the patient and the provider are able to do so, further evaluation for the true cause of the patient's symptoms is more likely to be successful.

The most common presentation of late Lyme disease in a large joint monoarticular arthritis, most typically involving one of the knees, although any joint can be affected (Fig. 32.8). Late Lyme infection occurs when manifestations of early localized infection and early disseminated infection go unrecognized and untreated. When earlier stages of Lyme disease are recognized and treated appropriately, late disease is prevented.

Monoarticular Lyme arthritis is often associated with arthralgias (joint pain without objective signs of inflammation) in other areas, but the finding of arthritis in multiple joints, especially involving the small joints of the hands and feet, should prompt an evaluation for etiologies other than Lyme disease.

Lyme arthritis can present abruptly. Rapid accumulation of joint fluid is uncomfortable and can severely limit the ability to use the affected joint. If the infection goes untreated, the arthritis typically cycles with a relapsing and remitting course that can last for years, with a significant toll of the health of the joint space. Lyme arthritis can present many weeks to many months after the initial infection, and while patients may retrospectively recall other symptoms of Lyme disease after the diagnosis is finally made, arthritis may be the first reported symptom of an infection. Lyme arthritis can usually be distinguished from septic bacterial arthritis fairly quickly since it tends to have a more indolent course and is associated with less severe local erythema and pain, minimal fever, and a lower synovial fluid cell count comprised predominantly of mononuclear cells rather than neutrophils. Although there is considerably overlap in expected synovial fluid cell counts in Lyme and septic arthritis, Lyme arthritis is a more likely diagnosis if fewer than 60,000 cells/microliter are present [23].

## 32.4 Laboratory Diagnosis

The recommended testing algorithm for patients suspected to have Lyme disease consists of a two-tier serologic test. First, a screening test is performed using either an enzyme-linked immunoassay (EIA) or an immunofluorescence assay (IFA). These screening tests are very sensitive in detecting total serum IgM and IgG antibodies that bind to *B. burgdorferi* antigens. Like many screening tests, the trade-off for such high sensitivity is that the EIA and IFA assays falter a bit in specificity, so confirmatory testing using an assay with excellent specificity is necessary to eliminate the false-positive screening test. All samples that test indeterminate or positive using either screening assay undergo reflex testing, meaning that the confirmatory test is performed automatically, using the Western blot technique. Unlike the screening EIA and IFA assays, the Western blotting technique identifies IgM and IgG antibodies that are generated against specific *B. burgdorferi* antigens. IgM and IgG antibodies produced by some individuals in response to antigenically similar non-borrelia proteins, such as the p41 flagellar antigen that is common to many Gram-negative bacteria, lead to the production of antibodies that recognize the p41 bacteria antigen whether the original antibody was in response to infection with *B. burgdorferi* or exposure to *Escherichia coli*. Currently, the proper interpretation of a Lyme Western blot result requires an evaluation of the IgM and IgG banding patterns using standardized criteria based on the number and type of antibodies detected. IgM banding patterns are assessed for three *B. burgdorferi* antigens including p24, p39, and p41, while IgG banding patterns are assessed for ten antigens including p18, p21, p28, p30, p39, p41, p45, p58, p66, and p93. A positive Western blot requires the presence of at least two of the three IgM bands or at least five of the ten IgG bands. While the presence of two or three bands fulfills the laboratory diagnostic criteria for the IgM Western blot, the overall specificity remains suboptimal, so care must be taken

to consider the result in the context of the clinical presentation. IgM is produced early during infection. IgM to IgG class switching with antibody affinity maturation occurs during the ensuing 4-week period. Patients who have already been symptomatic for 4 weeks or longer would be expected to have a positive IgM Western blot and may already have a positive IgG Western blot. If no IgG bands are present at all after 4 weeks of symptoms, the illness is not likely to be Lyme disease despite the results of the IgM testing. Patients who have been experiencing symptoms for longer than 4 weeks are expected to have a positive IgG Western blot if those symptoms are to be explained by Lyme disease ▶ Call Out Box 32.1.

Antibody testing used for the diagnosis of Lyme disease is most often performed on serum, but some clinicians will request antibody testing on cerebrospinal fluid (CSF) to aid in the diagnosis of neuroborreliosis. The absence of *B. burgdorferi*-specific antibodies in the CSF does not rule out central nervous system Lyme disease, and although a high CSF titer compared to the serum titer may suggest the presence of central nervous system infection, it is not diagnostic.



Assay to detect C6 peptide have shown promise as both a screening and confirmatory diagnostic test for Lyme disease. Some data suggest that a positive EIA followed by positive C6 peptide test, or a positive C6 peptide test followed by a positive Western blot, may be at least as sensitive and specific for the diagnosis of Lyme disease as is the traditional EIA/Western blot two-tier testing method, but results vary [24–28]. A potential advantage for C6 peptide testing is the ability to detect *Borrelia* strains from geographic areas other than North America [29].

Polymerase chain reaction-based testing designed to detect *B. burgdorferi*-specific DNA from a biologic sample has mixed utility. PCR performed on whole blood samples have a sensitivity of approximately 60%, but when used to test synovial fluid from patients suspected to have Lyme arthritis, sensitivity approaches 100%. Attempts to culture *B. burgdorferi* from blood or CSF are a sensitivity of approximately 30% and are generally discouraged in favor of serologic testing.

Other diagnostic tests, such as the detection of CD57+ lymphocytes or T-lymphocyte proliferative responses in the presence of *B. burgdorferi* antigens, are unproven as diagnostic aids [30]. The use of nonstandardized serologic testing, or PCR-based testing on biologic fluids that are not validated, such as urine, is discouraged. Clinicians should avoid using the results of nonstandard tests to make clinical decisions or to develop treatment plans for their patients.

## 32.5 Treatment

The recommended antimicrobial agents for the treatment of Lyme disease include doxycycline, amoxicillin, and ceftriaxone. Recommended alternatives for those who are allergic to or intolerant of all three first-line medications are azithromycin and cefuroxime. Most stages and most clinical presentations of Lyme disease can be treated with any of the recommended agents, with a few notable exceptions.

Doxycycline is the antibiotic of choice for the treatment of Lyme disease and is currently recommended for all stages of infection. A 14-day course of treatment is sufficient for early localized and early disseminated disease, including Lyme meningitis [31–33]. Some clinicians use longer durations for late disseminated disease (21–28 days). Doxycycline is also effective for the treatment of anaplasmosis, a Rickettsial infection that can be transmitted by the same *Ixodes* ticks that transmit Lyme disease.

Amoxicillin is effective in treating Lyme disease and has long been considered the drug of choice for the treatment of children under the age of 8 years, due to concerns that the use of doxycycline could stain permanent teeth. Concerns regarding the potential for this side effect are based on experience using tetracycline (rather than doxycycline) in young children. Furthermore, studies have shown that children who have been administered doxycycline for the treatment of Rocky Mountain spotted fever never developed dental problems [34, 35]. Many clinicians remain wary about using doxycycline in very young children, but current expert opinion favors its use for the treatment of Lyme disease [36–38]. Amoxicillin has not been studied for the treatment of Lyme meningitis, so doxycycline may be a fine alternative to a full 14-day course of treated with intravenous ceftriaxone.

Intravenous ceftriaxone is recommended for the treatment of Lyme encephalitis and Lyme carditis with clinically significant heart block, at least until the conduction defect resolves. Ceftriaxone is also an option for the treatment of Lyme meningitis, although recent clinical guidelines reflect the finding that oral doxycycline appears as effective in treating uncomplicated Lyme meningitis, without the risks associated with placement of a central venous catheter to administer a 2-week course of intravenous antibiotics [31–33] [▶ Call Out Box 32.3].

Studies on the pathophysiology of Lyme arthritis have revealed a substantial contribution of autoimmunity in the disease process, which has important clinical implications [39–41]. Several autoantibodies have been demonstrated in the synovial fluid of patients with Lyme arthritis. These antibodies persist long after antibiotic therapy killed the organism. It has been known for some time that Lyme arthritis can persist or recur after a 28-day course of antibiotic therapy. Historically, clinicians have used repeat courses of antibiotics, often escalating to prolonged courses of intravenous ceftriaxone. Currently, the vast majority of these patients are better served by management with anti-inflammatory medications and, if necessary, with repeated aspiration of excess joint fluid to improve joint function and comfort.

**Call Out Box 32.3**
Doxycycline is the antibiotic recommended for the treatment of most patients with Lyme disease, including those with Lyme meningitis. Ceftriaxone is recommended for the treatment of symptomatic Lyme carditis and for the rare cases of Lyme encephalitis.

## 32.6 Complications and Controversies

Without question, the biggest controversy surrounding Lyme disease centers around the concept of "chronic Lyme disease" (CLD) [42]. Patients with CLD are hypothesized to have persistent or latent Lyme infection with bacterial organisms that have evaded both the immune response and highly effective antimicrobial therapy. The theory is based, at least in part, on the experiences of patients with persistent yet ill-defined and nonspecific complaints of fatigue, myalgias, headache, and neurocognitive difficulties such as poor concentration and/or short-term memory problems sometimes collectively referred to as "brain fog." A small percentage of patients who have been diagnosed with and treated for Lyme disease do indeed experience chronic symptoms, a condition referred to as "posttreatment Lyme disease syndrome" (PTLDS). The risk for developing PTLDS does appear to be greater among patients who were not diagnosed and treated for their original Lyme diagnosis in a timely manner [43–45]. Clinical trials designed to evaluate any potential benefit of treating patients with PTLDS with prolonged courses of antibiotics for have not shown any lasting benefits [46–48]. Some patients have had documented reinfection with genetically distinct strains of *B. burgdorferi*, but chronic, ongoing infection has never been documented [49]. The pathogenesis of PTLDS symptoms is unclear, and several studies point out that the actual prevalence of symptoms described with PTLDS is similar to symptoms commonly experienced throughout the general population [50, 51], calling into question whether the syndrome is causally related to the prior Lyme infection at all.

Even more curiously, many patients diagnosed with ongoing Lyme infection or "CLD" do not have any evidence of a documented infection with *B. burgdorferi* at all! Some providers, self-identified as "Lyme experts," incorrectly argue that serologic testing for Lyme disease is insensitive and unreliable using the example that when a patient with an ECM rash is tested, they often have negative results. In fact, as discussed earlier, the timeline of antibody production is such that ECM may be present for several days to a week before any patient has evidence of seroconversion. Logic, medical evidence, and experience dictate that something other than Lyme disease is causing this spectrum of illness since it (a) presents atypically when compared to classic Lyme disease, (b) is undetectable using validated testing algorithms, (c) is unresponsive to conventional therapy known to eradicate the organism, and (d) is associated with common vague symptoms that are frequently experience by the general population. Despite such logic, patients who are experiencing debilitating, medically unexplained symptoms and who become desperate for relief turn to dubious diagnosticians who are providing unnecessary, ineffective treatments for an infection that has long been cured or was never present at all. Patients who seek such treatment often do so at their own personal cost since insurance carriers deny payments for such unusual treatments, and/or the medical practice they turn to will only accept payment directly from the patient [► Call Out Box 32.4].

**Call Out Box 32.4**
Testing for Lyme disease is recommended for patients with presenting complaints that are consistent with early disseminated or late Lyme disease. Clinicians are discouraged from performing testing for Lyme disease in patients with chronic, non-specific symptoms such as fatigue, malaise, and myalgias to avoid the potential for misinterpretation of false-positive results or inadvertently conveying to the patient that Lyme disease is a logical explanation for their symptoms.

There is a great deal of concern among some people that Lyme disease is a chronic, untreatable condition and a diagnosis to be feared. This assessment is fueled by those struggling with or pursing a diagnosis of "chronic Lyme disease."

There are definite risks associated with the inappropriate treatment of patients incorrectly diagnosed with having Lyme disease. Combination, prolonged antimicrobial therapy increases the risk of antibiotic-associated side effects, including *Clostridium difficile*-associated colitis [52]. Placement of percutaneous intravenous catheters for systemic antibiotic administration can result in deep thrombus formation, catheter-associated bloodstream infections, or other complications that require medical attention. The likelihood that a patient will develop a complication under such circumstances increases with time [48, 53–56].

**Case Study**

**Practical Examples**

1. A 5-year-old boy is evaluated for an "infected bugbite." his father noticed a tiny red mark on his arm a few days ago and now reports spreading erythema in the same area. The boy has had fevers and a decreased appetite but is otherwise well. On physical examination, he has a well-demarcated circular, macular rash with central clearing and a smaller red "bull's-eye" in the center on the skin of his right upper arm. The family resides in a wooded area in the state of Connecticut and has frequently encountered ticks on themselves and their family pets.

   This young man has erythema chronicum migrans based on clinical diagnosis. Testing for Lyme disease is unnecessary, and empiric treatment for early localized Lyme disease should be started. Traditionally, children under 8 years of age needing treatment for a diagnosis Lyme disease were recommended to receive amoxicillin rather than doxycycline due to concerns about potential tooth enamel staining from tetracyclines. This concern appears to be unfounded when doxycycline is used instead of tetracycline, but amoxicillin remains a reasonable treatment choice in the young age group, because it works, it is generally very well tolerated, and the suspension formulation has a favorable palatability profile.

2. A 30-year-old women complains of fatigue, malaise, and "joint aches", but no arthritis. She was diagnosed with early disseminated Lyme disease 1 year ago during an episode of aseptic meningitis. Serologic testing for Lyme disease at that time revealed a positive Lyme EIA with a positive confirmatory Western blot where ten out of ten IgG bands were detected. The woman was treated with a 2-week course of intravenous ceftriaxone, and her symptoms of meningitis resolved completely. Six months later, she sought medical advice for new symptoms of fatigue, malaise, and myalgias. Over the past 4 months, she has received treatment from a naturopath who diagnosed her as suffering from "chronic Lyme disease." Her naturopath informed her that she is "positive for Lyme in her blood and urine." You review the test results, noting that they were performed in an uncertified laboratory. Serologic testing for the presence of Lyme antibodies showed that several bands were present on Western Blot (without a prior EIA/ELISA screen). A polymerase chain reaction test performed on urine looking for DNA "fragments" of *Borrelia* species was reported to be positive. The report from the urine testing also lists "positive" findings for *Babesia* species and *Bartonella* species DNA fragments, but her serum antibody tests for those pathogens are reported to be negative. She states that this is her 13th week taking oral doxycycline, azithromycin, and atovaquone, but has not noted any improvement in her symptoms.

   The scenario presented is not uncommon. Diagnostic testing for Lyme disease in the setting of chronic non-specific symptoms is strongly discouraged for several reasons. In this case, a clear understanding of the nuances of using serologic testing for infectious disease diagnoses would have led an astute clinician to conclude that the presence of Lyme antibody was best explained by the patients classic Lyme illness 1 year earlier, and not a logical explanation for her current symptoms. Non-approved testing modalities are also associated with high false-positive rates, rendering them unnecessary and unhelpful in guiding a patient's diagnosis or treatment. The patient in the vignette should be advised to stop taking the antimicrobial medications she has been prescribed and have her symptoms reassessed.

3. A 25-year-old man is evaluated with a complaint that he sprained his knee. He woke this morning with a painful, swollen right knee. He does not recall any specific injury that might explain his symptoms but is an avid runner. He reports low-grade fevers and is now favoring his swollen knee but feels well otherwise and denies any other recent medical problems. He has no recollection of a tick bite but states that he frequently pulls ticks off of his pet dog. Joint fluid that is withdrawn by arthrocentesis appears slightly cloudy fluid. An hour later the laboratory reports a synovial fluid cell count of 45,000 cells/microliter and a Gram stain report of 3+ leukocytes and no bacteria. A complete blood count with differential is normal, and biomarkers of inflammation are only slightly elevated with an erythrocyte sedimentation rate of 25 mm/hr. (normal <20) and a C-reactive protein of 6 mg/L (normal <3). Bacterial cultures are pending. After aspiration of the joint fluid, the patient's range of motion and pain score are much improved.

   This case description is typical for Lyme arthritis. The likelihood of a bacterial septic arthritis is low based on the patient's lack of systemic signs or symptoms, fairly mild local signs and symptoms, a relatively low cell count in the joint fluid, and near-normal erythrocyte sedimentation rate and C-reactive protein. Serologic testing for Lyme disease should be requested to confirm the clinical diagnosis. Treatment with doxycycline could be initiated based on the strong clinical suspicion of Lyme arthritis, while all pending laboratory results (including the joint fluid culture) are followed until final results are available.

   The patient should be advised that even after effective antibiotic therapy, persistent or recurrent joint effusions may occur. Symptomatic management, including the use of nonsteroidal anti-inflammatory medications, such as ibuprofen or naproxen, is appropriate. Occasionally, recurrent joint aspiration is required to provide symptomatic relief. Extending or repeating antibiotic courses are no longer recommended for the treatment of prolonged or recurrent symptoms of Lyme arthritis. Retesting "to ensure the infection has cleared" is also not recommended since all available serologic tests will continue to show the presence of Lyme-specific antibodies for at least several years after then infection.

4. An 18-year-old woman presents with 25 days of recorded fever between 38.7 °C and 39.5 °C at least once daily. During this period of time, she has experience extreme fatigue. She points out nontender swollen lymph nodes in her neck and states that she had some facial and forehead swelling during the first week of her illness. She underwent an evaluation at a local urgent care center 3 days ago because she developed labial ulcers. Testing for herpes simplex infection was negative. At that time, she also had several blood tests performed including serologic testing EBV-associated infectious mononucleosis, Lyme disease, and human immunodeficiency virus. She received a telephone call this morning informing her that she had both "mono and Lyme" and was advised to see her primary care provider for treatment and follow-up. You review the laboratory test results. A heterophile antibody test performed to screen for EBV-associated infectious mononucleosis is reported to be positive. The cell differential of the complete blood count showed the presence of 22% atypical lymphocytes. The results of Lyme testing reveal an indeterminate result for the EIA, with two out of three IgM bands and zero out of ten IgG bands present on Western blot.

   The case described is most consistent with acute infectious mononucleosis caused by Epstein-Barr virus (EBV) infection with a false-positive Lyme antibody test. B-lymphocytes are the primary target during acute infection with EBV. One of the many immunologic sequelae is a polyclonal activation of B-lymphocytes. Transformation of B-lymphocytes into plasma cells with subsequent immunoglobulin synthesis and secretion results in the production of large amounts of IgM and IgG that lack any specificity. Due to the polyclonal nature of the phenomenon, individuals regularly produce antibodies that lead to falsely positive serologic tests for Lyme disease or other commonly used diagnostic studies. Moreover, the patient described in the vignette has been symptomatic for nearly a month and would therefore be expected to have IgG bands detected on the Lyme Western blot. From the clinical perspective, the patients constellation of symptoms are typical for acute mononucleosis and lacking in any of the classic features of early disseminate Lyme disease fever. If a concern remains, then repeat Lyme testing could be offered after an additional 4-week period.

## 32.7 Exercises

Please refer to the supplementary information section for answers to these exercises.

1. A patient presents with a history of well-documented Lyme arthritis treated successfully a year ago with a 4-week course of oral doxycycline. He had been symptom-free for over 10 months but now presents with new onset of knee effusion and pain, concerned that "my Lyme infection didn't go away." Discuss the evaluation and treatment of this patient and the kinds of anticipatory guidance that might be offered. How might you prove or disprove that he has developed Lyme disease again in this situation?

2. A 5-year-old girl is hospitalized with Lyme meningitis. She has been receiving intravenous ceftriaxone and is now feeling well enough to be considered for hospital discharge. What options are appropriate to complete her 14-day antibiotic course? Describe the benefits and risks for each?

3. A 7-year-old boy from upstate New York is seen in the emergency room for "persistent Lyme" according to his parents. He was diagnosed with Lyme disease 3 weeks ago when he presented to his pediatrician with a classic erythema chronicum migrans rash. At the time, his parents requested testing for Lyme disease, but the pediatrician explained that blood work was unnecessary and treated him with a 14-day course of amoxicillin. The rash resolved quickly, but the child continued to have daily fevers to 38.5 °C, fatigue, decreased appetite, and headache. He has not developed any respiratory of gastrointestinal symptoms, has never had joint swelling or pain, and has not developed a new rash. The parents again request that he be tested for Lyme disease and are insistent that he be hospitalized and treated with intravenous antibiotics. Discuss the various possibilities that could explain the boy's ongoing symptoms. What laboratory tests would you request and why? In the emergency room setting, the utility of serology- and PCR-based diagnostic tests is limited, so what information might be gained from the results of other routine laboratory tests?

## 32.8 Summary

Lyme disease is caused by the bacterium *Borrelia burgdorferi* and is transmitted by *Ixodes scapularis* and related ticks in the United States. The geographic range of the disease maps to the locations of the tick vectors and its usual mammalian hosts, the white-footed mouse and the white-tailed deer. Lyme disease has clinically distinct and clearly recognizable stages: early localized, early disseminated, and late disease. Treatment of clinically recognized early localized disease, erythema chronicum migrans, is prescribed without the need to perform diagnostic testing. The laboratory diagnosis of Lyme disease should be pursued for suspected early disseminated and late stage Lyme disease using the standard two-tiered approach. Doxycycline is the treatment of choice for most cases of Lyme disease, but amoxicillin or ceftriaxone may be used in the appropriate setting. The total length of treatment is based on the clinical presentation ranging between 14 and 28 days total.

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# Rocky Mountain Spotted Fever and Other Rickettsioses

## Fever, Headache, and Rash After Traveling to, or Living in an Endemic Area

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## 33.1 Introduction

Spotted fevers are a group of diseases caused by closely related bacteria, the *Rickettsia*. These infections are spread to human beings via bites of ticks, mites, or fleas. The hallmark of the disease process is vasculitis. Rocky Mountain spotted fever (RMSF) is the most common tick-borne rickettsial infection in the United States caused by the bacteria *Rickettsia rickettsiae* [1]. It results in direct small vessel injury and presents with fever, headache, and a characteristic rash. It is a serious infection with a case fatality rate up to 10% if left untreated.

Rickettsiae are considered emerging pathogens in many parts of the world and cause a wide-spectrum of illnesses [2–5]. Other rickettsial infections include *Rickettsia parkeri* infection, rickettsialpox, African tick bite fever, North Asian tick typhus, lymphangitis-associated rickettsiosis, Mediterranean spotted fever, Queensland tick typhus, Flinders Island spotted fever, Japanese spotted fever, tick-borne lymphadenopathy, Far Eastern spotted fever, and flea-borne spotted fever. These infections pose a challenge of early recognition as symptoms can be non-specific. The infections listed above are curable with antibiotic therapy of which tetracyclines are the most effective.

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## 33.2 Rocky Mountain Spotted Fever (RMSF)

RMSF gets its name from the initial epidemiological description in the Rocky Mountain region of the United States. The bacteria is named after Howard T. Ricketts, the first person to link this infection to wood ticks.

## 33.3 Historical Aspects

RMSF was recognized in late nineteenth century in the Bitterroot Valley of Western Montana near the Idaho border. It was described as "the so-called spotted fever of Idaho" by Edward E. Maxey [6]. After the initial reports in 1899, RMSF was soon identified throughout the Rocky Mountain States. Howard T. Ricketts provided the epidemiological link of this spotted fever with wood ticks through his guinea pig model of the disease. The organism was later identified by Simeon Burt Wohlbach in 1916, who chose to name it after Dr. Ricketts.

Certain aspects of the natural history of RMSF are not clear. For example, at the time of initial discovery in the pre-antibiotic era, the mortality in Idaho was 5–7%, whereas in Bitterroot Valley of Montana was 70%. The molecular basis for this difference in the virulence and mortality remains unclear [7]. Over the last century, the epidemiology of RMSF has evolved. It was initially regarded as a predominant disease in the Rocky Mountains region which is a belt of contagious states including Oklahoma, Arkansas, Missouri, Tennessee, and North and South Carolina [8]. Cases are no longer limited to the Rocky Mountain States but instead are now reported all across the Americas with most cases reported in the Southeastern and South Central states.

## 33.4 Pathogen Characteristics

*R. rickettsii*, the causative agent of RMSF, is a small (0.3–1 μm) nonmotile pleomorphic gram-negative coccobacillus. It is an obligate intracellular bacterium that resides in the cytosol and less commonly in nuclei of the host cells and divides via binary fission. It lacks the intrinsic ability to metabolize carbohydrates and amino acid substrates and derives energy from host adenosine triphosphate, ATP [9].

Rickettsiae are difficult to stain with ordinary bacterial stains but are readily stained by the Gimenez method or with acridine orange.

Rickettsiae exhibit a large family of surface proteins that are a major source of antigenic differences. Among these, OmpA and OmpB contain epitopes that are targets of humoral immunity and are the antigenic basis for serotyping [10].

## 33.5 Epidemiology

RMSF cases are reported throughout the United States, as well as in Canada, Mexico, Central America, and parts of South America. Confirmed and probable cases are reported through the National Notifiable Disease Surveillance System. Within the United States, the disease is most prevalent in the Southeastern and South Central states (Fig. 33.1a). The distribution of RMSF parallels tick activity during peak season.

***Vector*** - The principal vectors of *Rickettsia rickettsii* are the (i) American dog tick *(Dermacentor variabilis)*, (ii) Rocky Mountain wood tick *(Dermacentor andersoni)*, and (iii) brown dog tick *(Rhipicephalus sanguineus)* (Fig. 33.1b, i, ii, iii). The geographic distribution of RMSF follows the areas in which these ticks are found. The American dog tick is found in Eastern and Central United States [11], the Rocky Mountain wood tick is found in the western United States, and brown dog tick is found in the Southwest (Arizona) [12] and along the United States-Mexico border. *Amblyomma imitator* is a vector for *R. rickettsii* in Mexico. *Amblyomma cajennense* and *Amblyomma aureolatum* are the vectors in South America [13].

Infection rates among populations of ticks are variable; for example, in *Dermacentor*, only a small portion of ticks (usually 4%) carry any rickettsiae, and less than 1 in 1000 ticks carry virulent *R. rickettsii* [14]. Other factors which play a role in fluctuation of the tick populations and the prevalence of RMSF include humidity, climatic variations, human activities altering the vegetation, and the use of insecticides [15].

***Distribution*** - About 60% of the cases occur in the contagious states of Oklahoma, Tennessee, Missouri, Arkansas, and North Carolina. Recently, RMSF cases have been identified in an area of eastern Arizona, where the disease had not been previously seen with 320 cases reported with a case fatality rate of about 10% between 2003 and 2014. The tick responsible for transmission of *R. rickettsii* in Arizona is the brown dog tick, which is found on dogs and around homes. Almost all of the cases occurred within communities with a large number of street dogs.

***Prevalence*** - RMSF has been a nationally notifiable condition since the 1920s under the category of Spotted fever rickettsiosis. The incidence of RMSF has increased in the past few years from an incidence of 1.8 per million people in 2000 to 14.3 per million individuals in 2012, which is

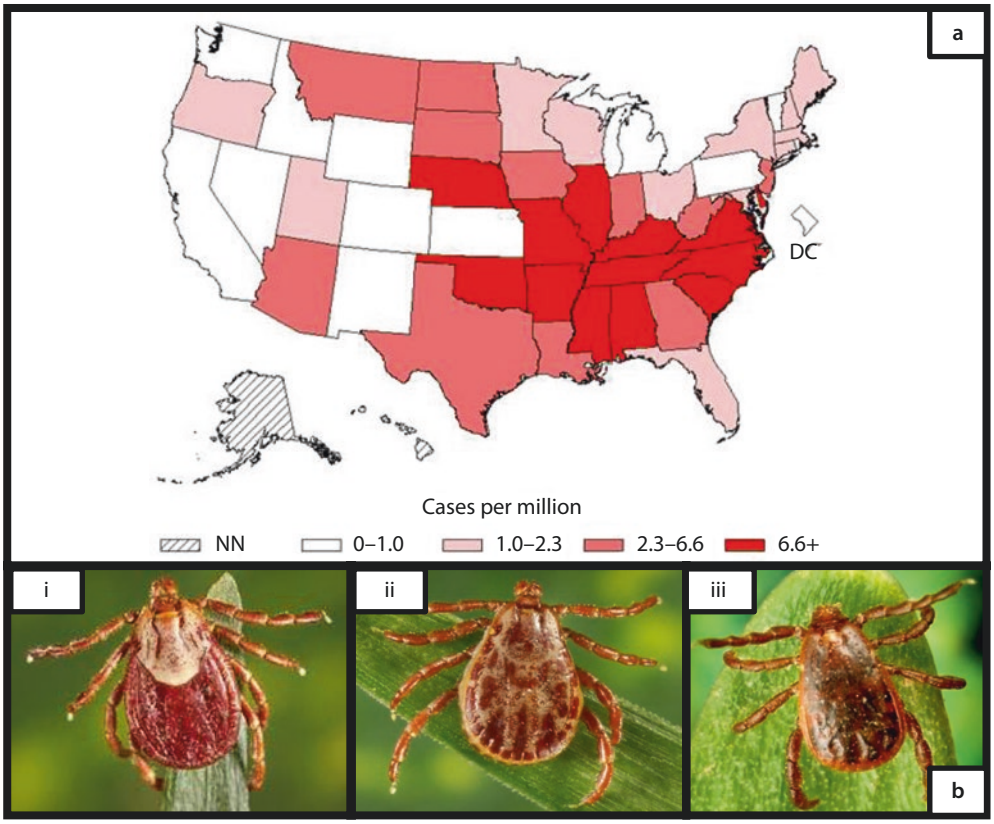


**Fig. 33.1** **a** Incidence (per million population) for SFR (Spotted fever rickettsiosis) in the United States for 2014. (*NN* not notifiable). **b** (i) American dog tick (*Dermacentor variabilis*), (ii) Rocky Mountain wood tick (*Dermacentor andersoni*), and (iii) brown dog tick *(Rhipicephalus sanguineus*). (Courtesy of CDC)

approximately 4500 new cases each year. Local prevalence in highly endemic areas, such as North Carolina, has been as high as 14.59 per 100,000 [16–18]. Tribal lands in Arizona have also been found to be highly endemic areas for RMSF. The incidence of infection may decrease in one area and increase simultaneously in another region [19].

***At-risk population*** - Individuals with either occupational or recreational exposure to ticks, such as those working with animals, are at higher risk. In the Southern states, the incidence is highest in children, adults 60 to 69 years old, and persons who are known to be exposed more often to ticks. In the Western mountainous states, because of transmission by the wood tick *D. andersoni*, a higher proportion of men contract the disease due to occupational exposure [20].

***Seasonality*** - RMSF is most common in spring and summer months when ticks are most active [21]. In Arizona, cases transmitted by the vector *Rickettsiae sanguineus* peaked in July and September [22]. Rarely cases in winter months have been reported in the Southern United States [23].

***Case fatality rates*** - This varies from year to year, but there has been an overall decreasing trend from 28% case fatality in 1944 to less than 1% case fatality beginning in 2001. Overall mortality rate without treatment is 5–10%. In a series of 7796 cases reported to the US Centers for Disease Control and Prevention, the overall case fatality rate declined from 2.2% in the year 2000 to 0.3% in 2007. This rate remained essentially unchanged from 2007 to 2010 [24]. However, mortality rate is higher in certain groups: males, individuals over 50 years old, children between 5 and 9 years old, individuals who do not realize they have been bitten by a tick, or those in whom initiation of antibiotics occurs after the 5th day of symptoms [25, 26].

***Transmission*** - *D. variabilis*, *D. andersoni*, and *R. sanguineus* ticks are all members of the Ixodidae family (hard ticks) and are vectors for *R. rickettsii*. Ticks, rodents, and other small mammal hosts serve as a reservoir. There have been rare instances of laboratory-acquired RMSF from aerosolization, as well as through blood transfusions.

The most common mode of transmission is when a tick attaches to a human to start feeding for a blood meal. The bite is painless and frequently goes unnoticed and may persist for 1–2 weeks. Ticks most commonly attach to the head, neck, and groin. *D. variabilis* prefers the head and neck. *R. sanguineus* more commonly attaches to the head in children but the rest of the body in adults [27]. Ticks in the Ixodidae family feed slowly, over the course of several days. Transmission of the bacteria from the tick to the human usually occurs at the attachment site, via saliva, regurgitated of gut contents, or feces [8]. Transmission may also rarely occur in the absence of attachment, when an infected tick is crushed and comes into contact with conjunctiva or broken skin.

Rickettsiae multiply in most organs and fluids within the tick, especially the salivary glands and ovaries. This leads to transmission while the tick is taking a blood meal. In addition, transmission occurs transovarially (from one generation of tick to the next) and rickettsiae are also able to survive throughout the various stages of a tick's life cycle, allowing transstadial (from one stage to the next) transmission.

## 33.6 Pathogenesis

*R. rickettsia* exhibits tropism for vascular endothelium. It infects the endothelial cells lining of small- and medium-sized blood vessels of all major tissues and organ systems.

The infection begins when an infected attached tick has fed for 4–6 h and injects rickettsiae from its salivary glands. They organism then spreads via lymphatics and small blood vessels to the systemic and pulmonary circulation.

At the target location, rickettsiae are internalized into the vascular endothelium. The plasma membrane of mammalian cells expresses Ku70, which serves as a receptor for the outer surface proteins of OmpA, OmpB, and sca 1 for *R. rickettsia* attachment and subsequent phagocytoses by the host cell. The organism degrades the vacuolar membrane and escapes into the cytosol as rickettsiae are obligate intracellular pathogens and require access to the cytoplasm to grow. Once in the cytoplasm, the organisms replicate by binary fission [28]. They use the actin to spread from cell to cell. They spread rapidly among the endothelial cells lining the vascular and lymphatic systems. As the cells become injured by the rickettsiae, they lose their attachment to adjacent cells, and the smooth vascular surface becomes increasingly permeable.

As the endothelial cells detach, small leaks in the capillary bed produce vascular permeability, microhemorrhages, localized edema, and local inflammation. Over time this process affects a wide variety of organs, including the skin, brain, lungs, kidneys, and liver. Eventually the combination of leakage, edema, and inflammation can produce organ failure.

The immune response to *R. rickettsia* involves perivascular lymphocytic infiltrates. Clearance of *R. rickettsii* is predominantly by cellular immunity, including cytotoxic T lymphocytes and interferon-γ. The immune response lyses the infected cells, an action that may be the primary means by which rickettsial infection causes cell injury. A broad range of antibodies are produced against *R. rickettsii*, and these antibodies appear to be the host's primary defense against reinfection.

The laboratory findings of RMSF reflect this diffuse vascular injury often with profound thrombocytopenia secondary to platelet consumption along damaged surfaces and mild to moderate hyponatremia. The hyponatremia is due to a combination of electrolyte shifts from the intracellular to the extracellular space, loss of sodium through excretion, exchange of sodium for potassium at the cellular level, and the syndrome of inappropriate antidiuretic hormone secretion [29].

## 33.7 Clinical Manifestations

The incubation period is approximately 1 week, with a range of 2–14 days.

***Early symptoms*** - The disease usually begins with fever (99–100% of the cases), myalgia, and headache (79–91%). The temperature is higher than 102 °F (38.9 °C) in almost two third of patients during the first 3 days. The incidence of reported myalgias and headache might be lower than expected given a high proportion of young children affected by this infection who are unable to communicate these symptoms [30]. In early infection, before appearance of the rash, gastrointestinal symptoms are prominent with nausea, vomiting, abdominal pain, and diarrhea suggestive of gastroenteritis or even a surgical abdomen. These non-specific symptoms of early infection can make diagnosis difficult.

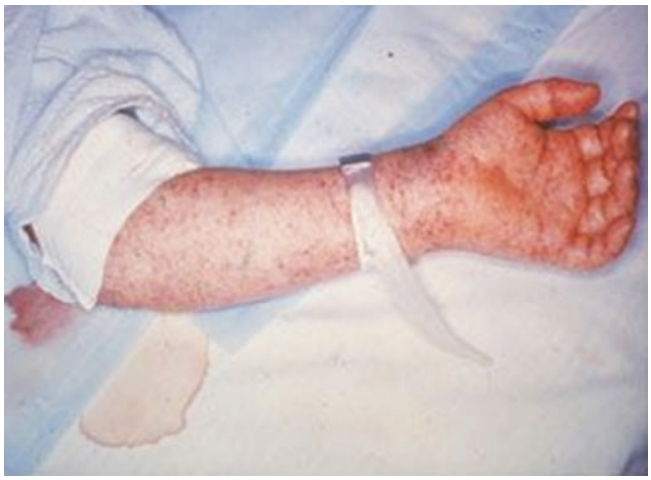

**Fig. 33.2** Rash in a child with RMSF. (Courtesy of CDC)

***Rash*** - The classic sign of RMSF infection is the rash, which appears in a small proportion of patients on the first day of the disease and in only 50% of patient during the first 3 days. It usually develops 3–5 days after the onset of fever and is present in 88–90% of all the patients (Fig. 33.2). The rash typically begins around the wrists and ankles but may start on the trunk or be diffuse at the onset. Involvement of the palms and soles is considered a typical feature but is present in only 36–82% of patients, and it occurs later in the disease. Skin necrosis or gangrene develops in only 4% of cases as a result of rickettsial damage to the microcirculation. Rocky Mountain "spotless" fever occurs more often in older patients and in black patients which may result in a delay in diagnosis.

***CNS symptoms*** - The headache is characteristically severe in nature. Meningismus and photophobia may be present and suggest meningitis. Cerebrospinal fluid shows pleocytosis in one third of patients, with either lymphocytic or polymorphonuclear predominance. CSF protein concentration is high in one third of patients, and CSF glucose concentration is low in only 8% of patients [31]. The presence of neurologic involvement is a sign of poor prognosis. In a series of cases of children with RMSF, 15% of survivors had neurologic deficits at discharge, including global encephalopathy, ataxia, and blindness.

***Other organs*** - Renal failure is an important complication in severe RMSF. Prerenal azotemia related to hypovolemia responds to intravenous hydration; however, acute tubular necrosis may require hemodialysis. Pulmonary involvement is suggested by cough, and radiologic changes may include alveolar infiltrates, interstitial pneumonia, and pleural effusion. Pulmonary edema may lead to poor gas exchange [32]. Echocardiographic studies reveal minimal myocardial dysfunction [33].

***Fulminant course*** - If left untreated RMSF can be fatal in 7–15 days after onset of symptoms. Fulminant cases result in death within 5 days. Several features account for the difficulty associated with the diagnosis of fulminant RMSF. The course is rapid, the rash may be absent or develop shortly before death, and antibodies do not have time to develop. Even the pathologic lesions even appear different, containing more thrombi and lacking the characteristic lymphohistiocytic component. Fulminant RMSF is more often seen in black males with glucose-6-phosphate dehydrogenase (G6PD) deficiency [34]. Mortality is also higher in the young and the elderly.

## 33.8 Laboratory Diagnosis

Anemia (observed in 5% to 30%) and thrombocytopenia are frequently seen in RMSF. In one case series the average platelet count at presentation was 128,000 cells/mm$^3$, and 41% had fewer than 100,000 platelets at initial presentation. Hyponatremia was observed in half of patients with RMSF. The median sodium concentration at presentation was 133 mEq/L, and 52% of children had a serum sodium concentration below 135 mEq/L [35]. The white blood cell count is generally normal, but increased quantities of immature neutrophils occur frequently. Increased concentrations of serum lactate dehydrogenase and creatine kinase are frequently present.

***Confirmatory testing*** - The most widely used test in the diagnosis of RMSF is the indirect immunofluorescence (IFA) assay. A confirmatory diagnosis requires a fourfold rise in titer between acute and convalescent sera collected 2–6 weeks apart. A "probable" diagnosis can be made on the basis of a single convalescent IFA titer of 1:64 or greater. The sensitivity is low in the first 10–12 days of illness, and a negative test does not rule out RMSF. However, the test is 94% sensitive by 14–21 days [36]. A few limitations of IFA assay include the presence of low-level antibody titers in a significant proportion of the general population in some regions, and the IgM level may remain elevated for months and is not highly specific for acute RMSF.

Polymerase chain reaction (PCR) is less established as a diagnostic method but can be performed on either tissue or blood. It is most useful very early in the course of disease before antibodies appear. Real-time PCR can be used to detect *R. rickettsii* DNA in acute whole blood and serum specimens. The specimen should preferably be obtained within the first week of symptoms and before or within 1 day of starting doxycycline. A negative result does not rule out RMSF infection.

A skin biopsy can be performed to sample the petechial lesions in acute infection and sent for either immunohistochemical staining or PCR testing. Immunohistochemical staining of biopsy material has been found to be 100% specific and 70% sensitive.

## 33.9 Differential Diagnosis

A high index of suspicion is required to diagnose RMSF during early disease. It should be considered in a child with characteristic fever and rash illness, who is residing in an endemic region or perhaps a traveler to a region with higher incidence of RMSF, particularly during peak season of summer. Given the high morbidity and mortality associated with untreated infection, treatment should be provided early in the course.

The differential diagnosis of RMSF includes other infections with fever and rash, especially those involving rash including palms and soles, i.e., enteroviral infection, secondary syphilis, West Nile virus, and less commonly meningococcemia. An enteroviral infection is typically seen in summer months, the child is relatively well-appearing, and the screening laboratory tests usually do not reveal significant derangements. In a sexually active individual, secondary syphilis can present with fevers and rash including palms and soles. Invasive West Nile virus causes maculopapular rash with petechial component. Sepsis, especially meningococcemia, should be considered in a toxic-appearing child presenting with fevers and a purpuric rash. Toxin-mediated gram-negative sepsis should be considered in an immunocompromised host with fever and rash.

Other tick-borne infections, such as monocytic ehrlichiosis or granulocytic anaplasmosis, can present strikingly similar to RMSF. However, ehrlichiosis usually is associated with leucopenia and thrombocytopenia, and rash is often absent. It should be kept in mind that tick-borne coinfections are possible in the same patient bitten by the same tick.

Other infectious and inflammatory entities such as acute infectious mononucleosis, parvovirus infection, roseola, scarlet fever, leptospirosis, and Kawasaki disease all have clinical features which can be confused with RMSF. If there is a history of travel, typhoid fever and dengue should be in the differential. The new *Phlebovirus* (Heartland virus) seen mostly in Missouri, and a new rickettsial species (*Rickettsia amblyommii*) seen in North Carolina, may present similarly to infection with *R. rickettsii*. Fever and rash can also be present with noninfectious conditions, such as drug reactions, and vasculitis.

## 33.10 Treatment

RMSF is a serious illness, and treatment should not be delayed in children with consistent clinical epidemiology while waiting confirmatory testing. *Doxycycline or other* tetracyclines are the treatment of choice. Treatment within the first 5 days of symptoms significantly reduces hospitalization, admission to ICU, and fatality as opposed to children who are treated after 5 days of illness [37, 38]. For children of any age, doxycycline is the drug of choice. The recommended dose for children weighing >45 kg (100 lb) is 100 mg every 12 h. For children weighing <45 kg, doxycycline is given at a dose 2.2 mg/kg every 12 h**.** Both oral and intravenous formulations are available in the United States. Doxycycline is preferred over other tetracyclines because of its reduced phototoxicity, safety in children with renal insufficiency, lower binding to calcium, and longer plasma half-life. The majority of children with uncomplicated infection defervesce within 1–2 days after initiation of doxycycline. The absence of clinical improvement within 72 h should suggest the need

to consider an alternate diagnosis even in patients with multiple organ damage. Doxycycline should be continued for at least 3 days after clinical improvement is seen. The usual duration of treatment is 7–10 days.

Some pediatricians are hesitant to use doxycycline in children less than 8 years of age [39, 40]. This is because of studies in children who received older tetracycline, oxytetracycline, or chlortetracycline during tooth crown calcification and developed enamel hypoplasia and discoloration, yellow, gray, or brown staining of permanent teeth. However no such observations are made with doxycycline, as available today.

*Chloramphenicol* is the only other antibiotic with demonstrated clinical efficacy against *R. rickettsia*. However, the oral form is no longer available in the United States and the parenteral formulation is being produced in limited amounts. In addition, epidemiologic data suggest that patients treated with chloramphenicol have a higher risk for severe illness and death compared to children treated with a tetracycline. Furthermore in vitro evidence suggests that chloramphenicol may not be effective treatment for infections caused by *Ehrlichia* and *Anaplasma* spp., which often manifest similar clinical syndromes to RMSF [41]. The pediatric parenteral dose of chloramphenicol is 50 to 100 mg/kg/day in four divided doses. It can result in reversible dose-related toxicities including bone marrow suppression and cardiomyopathy. Monitoring of serum levels is advisable when treating patients younger than 2 years, patients with hepatic disease, or people receiving therapy for more than 5 days. Peak serum levels of chloramphenicol should be maintained within the range of 10 to 30 μg/mL.



## 33.11 Prevention

Avoidance of tick-infested areas, such as grassy areas and areas that border wooded regions, is the best preventive measure. If a tick-infested area is entered, children should wear protective clothing, and tick repellents should be applied to clothes and exposed body parts for added protection. All pets should be treated for ticks according to veterinary guidelines. Parents should be instructed to inspect themselves, children, and pets after spending time outdoors to screen for ticks and remove them properly if found.

Prophylactic antibiotic therapy in asymptomatic people with a recent history of a tick bite is not warranted. Since tetracyclines are bacteriostatic drugs, presumptive therapy before onset of symptoms is unlikely to prevent infection and may instead result in a delayed onset of disease [42]. Children should not be tested or treated for RMSF until at least one symptom of illness is present. There is no licensed *R. rickettsii* vaccine available.

***Isolation Precautions*** - A child admitted to the hospital requires standard precautions of infection control.

## 33.12 Other Rickettsiosis

A number of other pathogenic rickettsiae cause disease in human (Table 33.1). They can be grouped based on antigenic and genetic properties:

1. Rickettsia of spotted fever group: This group accounts for most of the tick-borne rickettsioses and rickettsialpox, which is a mite-borne infection. RMSF is the prototype of this group. Other important spotted fever infections are discussed below.
2. The typhus group is comprised of two pathogens transmitted by insects. Epidemic typhus is caused by *Rickettsia prowazekii* and transmitted by the body louse. The murine typhus caused by *Rickettsia typhi* is transmitted by rat and cat fleas.
3. *Orientia*, the scrub typhus group, consists of only *Orientia tsutsugamushi* and is transmitted by the bite of chiggers.

## 33.13 Other Spotted Fever Group

This group comprises rickettsial disease other than RMSF. Spotted fevers have worldwide distribution and cause mild to life-threatening infections. Most people with a spotted fever other than RMSF develop fevers, headache, and an eschar. An eschar is a dark scab at the site of tick or mite bite. Doxycycline is the treatment of choice for all spotted fever infections, and all are obligate intracellular pathogens. The important members of this group are as follows:

***Rickettsia parkeri* infection** - It is regarded as an emerging rickettsial infection in the United States. The vector for *R. parkeri* is the Gulf Coast tick, *Amblyomma maculatum*. Most of the cases are seen in the Gulf Coast and Southeastern states. *R. parkeri* produces a mild spotted fever illness that may be difficult to clinically distinguish from mild RMSF. An important distinction is the presence of an eschar (Fig. 33.3) or a vesicular rash in *R. parkeri* infection as compared to RMSF [3]. There are also relatively less gastrointestinal symptoms in *R. parkeri*. The antibodies produced against *R. parkeri* cross-react with RMSF, so serologic assays in clinical use cannot distinguish them. Given this difficulty in distinguishing *R. parkeri* and RMSF, it is recommended to treat all cases of suspected R. *parkeri* as if they are RMSF.

**Rickettsialpox** - First described in New York City in 1946 by Susman as "Kew Gardens spotted fever" [43], rickettsialpox is caused by *Rickettsia akari* and is transmitted by the bite of the house mouse mite, *Liponyssoides sanguineus*. This mite passes the infection transovarially and can act as both the vector and the reservoir. Humans are typically infected by mouse mites after mouse extermination, which results in starving mites seeking alternative sources for a blood meal.

The bite is painless, and the incubation period is 9–14 days. The characteristic skin lesion is a painless red papule at the site of the inoculation which becomes vesicular over the next several days and eventually crusts, producing an eschar. Fever characteristically begins no more than 24 h before the development of rash.

**Table 33.1** Common rickettsial infections in humans: the spotted fever group, typhus fever and scrub typhus

| Group | Disease | Organisms | Vector | Clinical features | Treatment | Epidemiology |
|---|---|---|---|---|---|---|
| Spotted fevers | RMSF | *Rickettsia rickettsii* | Tick | Fever<br>Headache<br>Rash | Doxycycline | South Atlantic, Southeastern and South Central United States |
| | African tick-bite fever | *R. africae* | Tick | Fever<br>Headache Neck pain<br>Inoculation eschar (with regional lymphade-nopathy) | Doxycycline | Sub-Saharan Africa, West Indies |
| | Rickettsialpox | *R. akari* | Mite | Fever<br>Eschar | Doxycycline<br>Alternative: chloramphenicol (risk of serious adverse effects, oral form is not available in the United States) | Countries of the former Soviet Union, South Africa, Korea, Turkey, Balkan countries, United States (northeastern metropolitan centers) |
| | Queensland tick typhus | *R. australis* | Tick | | | Australia, Tasmania |
| | Mediterranean spotted fever or boutonneuse fever | *R. conorii* | Tick | Tache noire (black spot)<br>Bradycardia<br>Phlebitis<br>Fever | Doxycycline<br>Alternatives: clarithromycin, azithromycin, chloramphenicol, ciprofloxacin | Southern Europe, south and western Asia, Africa, India |
| | Flinders Island spotted fever, Thai tick typhus | *R. honei*, including strain "marmionii" | Tick | | | Australia, Thailand |
| | Rickettsiosis | *Rickettsia aeschlimannii* | Tick | Eschar | Doxycycline | South Africa, Morocco, Mediterranean littoral |
| Typhus fever | Epidemic typhus, sylvatic typhus | *R. prowazekii* | Human body louse<br>Flying squirrel ectoparasites possibly some ticks | High fever<br>Chills<br>Myalgias<br>Headache | Doxycycline<br>Alternative: chloramphenicol (when life-threatening allergy to doxycycline)<br>Treat louse-infected patients with cream or gel pediculicides | Central Africa, Asia. Central, North, and South America |
| | Murine (endemic) typhus, fleaborne typhus | *R. typhi* | Flea | Fever<br>Headache<br>Myalgias<br>Anorexia | Doxycycline<br>Alternatives: chloramphenicol or fluoroquinolones (may not be effective) | Tropical and subtropical areas worldwide |
| Scrub typhus | Scrub typhus | *Orientia tsutsugamushi* | Larval mite (chigger) | Eschar<br>Fever<br>Headache<br>Myalgias | Doxycycline<br>Alternative: azithromycin, rifampin, chloramphenicol | Asia-Pacific region from maritime Russia and China to Indonesia and North Australia to Afghanistan |

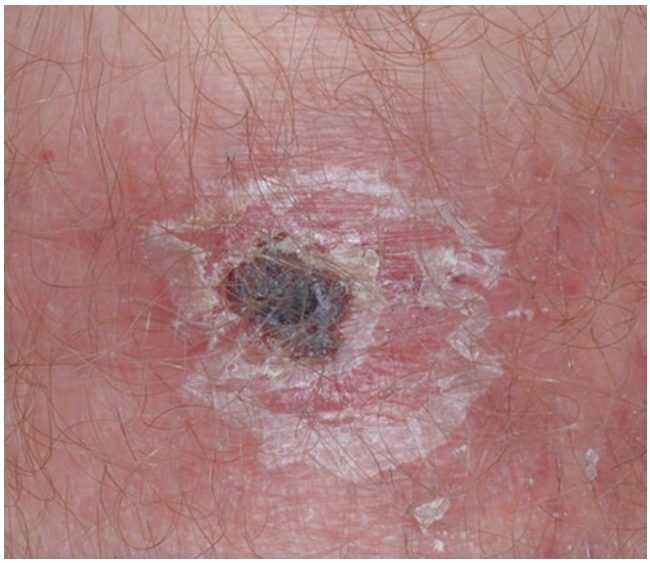

**Fig. 33.3** Eschar on patient with *R. parkeri* rickettsiosis. (Courtesy of CDC)



The diagnosis can be made by serology, use of immunohistochemical staining of skin biopsy, or PCR assay or culture of *R. akari* from the eschar. In terms of serology, a fourfold increase in serum antibodies to *R. akari* between acute and convalescent sera or a single titer of more than a 1:64 dilution is considered diagnostic. Doxycycline is the treatment of choice. Rickettsialpox is usually a mild self-limiting illness even without treatment, but symptoms may last 3 weeks if treatment is not administered early.

**Mediterranean spotted fever** - This infection is caused by *Rickettsia conorii*. Mediterranean spotted fever is also known as boutonneuse fever and Marseilles fever. It is associated with high mortality similar to RMSF. It is reported across a wide geographic region that includes not only the Mediterranean region but also parts of central and southern Africa, the Middle East, and central and south Asia. The only known vector is the brown dog tick, *Rhipicephalus sanguineus*. The incubation period ranges from 6 to 10 days. The onset of disease usually is abrupt, with high fevers which can continue for 6–12 days. Severe and unremitting headache is a typical feature of the disease in adults. On the other hand, headache is reported in less than one third of pediatric patients. The primary lesion is a black spot, named "tache noire" seen in 30–90% of cases. It develops at the site of inoculation, is not painful, and is rarely pruritic. It occurs most often on the head in children and on the legs in adults.

Diagnosis can be made by immunofluorescence of eschar early in the course of disease or by PCR on the skin lesion [44]. Multiple serologic tests are available to assist in diagnosis. An IFA assay for *R. conorii* is commercially available. Doxycycline is the treatment of choice. An alternative regimen is clarithromycin or azithromycin. Other effective therapies include chloramphenicol and ciprofloxacin.

**African tick bite fever** - Another prominent member of the spotted fever group is *Rickettsia africae*. It is one of the most common acute febrile illnesses seen in travelers to southern Africa. It is also endemic on some eastern Caribbean islands. Cattle ticks from the genus *Amblyomma* are responsible for transmission. The clinical hallmarks are fever, headache, neck muscle myalgias, and an eschar with regional lymphadenopathy. Almost half of patients have multiple eschars that ascend along the lymphatic drainage. African tick bite fever is a benign infection and is self-limited in most cases. Doxycycline results in more rapid resolution.

Many other *Rickettsia* species are known to cause infection in humans. *Rickettsia japonica* is the etiologic agent of Japanese spotted fever, *Rickettsia sibirica* of Siberian tick typhus, and *Rickettsia australis* of Queensland tick typhus. Ticks are the vectors, and dogs are the principal mammalian reservoir for these species. *Rickettsia felis* is transmitted by fleas, and its natural reservoirs are the opossum and the cat. A newly recognized tick-borne disease in Europe is a *Rickettsia slovaca* infection, for which the wild boar is the main host. The diseases caused by these and other rickettsial species have similar clinical, pathologic, and epidemiologic patterns. As with other rickettsioses, doxycycline is the preferred therapy.

## 33.14 Typhus Group

It is a louse-borne infection caused by *R. prowazekii*. It is a pathogen of historical importance and was the culprit of many outbreaks in the past. Most outbreaks have struck during times of war due to overcrowding conditions. Outbreaks of typhus occurred throughout the world during the nineteenth century, famously devastating Napoleon's army. During World War II, typhus killed tens of thousands of people as a result of the deplorable conditions in the Nazi concentration camps.

The development of dichlorodiphenyltrichloroethane (DDT) in the 1950s resulted in a dramatic worldwide decline in typhus. Since then, it has reemerged predominantly in highland regions of sub-Saharan Africa and to a lesser extent Central and South America. Rwanda, Burundi, and Ethiopia have been particularly affected as a result of the coexistence of poverty and war. In the United States there have been at least 30 cases since 1976 [45].

The human body louse, *Pediculus humanus corporis*, is the vector for epidemic typhus. The human body louse inhabits clothing, from which it will take blood meals from its host. Colder conditions, in which people wear extra clothing, increase louse habitat. Lice will not survive for long away from a suitable host, so impoverished persons who do not have changes of clothing will be most heavily infested. Under crowded and unhygienic conditions, lice will readily pass between people.

Illness begins after a 10- to 14-day incubation period. An initial period of malaise is followed by high fever, headache, and rash. Headache is common and may be severe or intractable. Cough is also a frequent complaint. The rash usually appears initially on the trunk within the first 3–5 days; it spreads peripherally to the extremities and usually spares the face, palms, and soles. Mortality was as high as 60% in the pre-antibiotic era and is higher in malnourished populations and the elderly. With appropriate antibiotics, the mortality is approximately 4%. Recrudescent infection, known as the

Brill-Zinsser disease can occur years after the primary infection if it is not eradicated.

Typhus is often diagnosed by serology. A fourfold rise in IgG antibody titer is considered diagnostic. Shell vial culture can detect *R. prowazekii* from blood specimens. Doxycycline is the treatment of choice for epidemic typhus. Therapy is given until the patient is afebrile for at least 3 days and clinical improvement is evident; the usual duration is 7–10 days. Chloramphenicol is an alternative agent for those with a serious contraindication to doxycycline. Fluoroquinolones have in vitro activity, but there has been a treatment failure with ciprofloxacin resulting in death.

It is also known as endemic typhus and is a flea-borne infection primarily of rats, opossums, and cats. The disease occurs worldwide, especially in warm climates where rats or opossums are abundant. The incidence in the United States is unknown. It is estimated that about 0.6% of children in South Central states have *R. typhi* titer of greater than 1:64. The seroprevalence in southeastern Texas may be as high as 15% [46]. These figures suggest that murine typhus is considerably underrecognized in certain regions.

*R. typhi* infection is a vector-borne zoonosis that persists in a flea-mammal cycle in nature. Murine typhus is clinically similar to epidemic typhus, but it is milder and of shorter duration. Symptoms develop after a 5- to 10-day incubation period, although an antecedent flea bite is not always reported. The classic triad of fever, headache, and rash is seen in half of patients. Children who receive appropriate antibiotics undergo defervescence in 1–3 days.

A fourfold change in titer between acute and convalescent sera is diagnostic. Immunohistochemical staining or PCR analysis of amplified gene product of tissues and culture, available through the CDC, also can be used for confirmation.

Doxycycline is the treatment of choice for murine typhus. Chloramphenicol is an alternative in patients with a contraindication to tetracyclines. Treatment should be continued for at least 3 days after defervescence and evidence of clinical improvement typically 3–7 days.

Scrub typhus is a chigger-borne disease caused by *Orientia tsutsugamushi* that exclusively occurs in the Asia-Pacific region. The organism was formerly a member of the genus *Rickettsia*, and in 1995 it was reclassified to the novel genus *Orientia* on the basis of distinctive phenotypic and genetic features [47].

Scrub typhus is widely distributed throughout central, eastern, and southern Asia. Humans are most likely to encounter chiggers in rural areas. Travelers engaged in outdoor activities, such as camping and trekking, are at risk for acquiring scrub typhus; some of these individuals do not become clinically ill until after return to their home country.

Trombiculid mites from the genus *Leptotrombidium* are the vectors for scrub typhus. Wild rodents, particularly rats, are the preferred host for chiggers and are important in the ecology of scrub typhus. In more than half of cases, the initial mite bite lesion develops into a necrotic eschar. The eschar site in adults is truncal, and in children, eschars are seen commonly in moist intertriginous areas such as the genitalia and perineum.

The mainstay of scrub typhus diagnosis is serologic testing. The "gold standard" is the indirect IFA assay, and an eschar PCR assay is also available. Doxycycline is the treatment of choice. Children have responded well to treatment for 4–7 days. Doxycycline is rickettsiostatic, and patients with scrub typhus who are treated in the first week of illness can require sporadic short courses of antibiotic therapy for prevention of relapse. Chloramphenicol, azithromycin, and rifampin are alternatives.

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# Malaria

## Fever and Pallor While Living in, Traveling to, or Returning From Just About Anywhere in the Tropics or Subtropics

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**Learning Objectives**

- Review the epidemiology, life cycle, and pathogenesis of *Plasmodium* spp.
- Become familiar with signs and symptoms of malarial illness.
- Understand morbidity and mortality associated with the condition.
- Understand the basic steps in the diagnosis and management of malaria.

## 34.1 Introduction to the Problem

"Tropical diseases" have increasing significance across the globe for a host of reasons that range from greater movement of people with potential to spread disease to climate changes that cause shifts in vector biology creating new ecosystems that can support emerging diseases in areas that were not previously endemic. The globe has become a small place with the potential now for travel between the most distant points within 24 hours. With fewer boundaries to contain vectors and disease, it is important for clinicians to remain aware of diseases previously restricted to endemic regions and to habitually develop broad differential diagnoses that include those problems. Malaria is an excellent example.

The World Health Organization (WHO) tracks progress on the prevention and treatment of malaria across 91 endemic countries. Nearly half of the world's population is at risk for developing malaria because of where they live (Fig. 34.1). Globally, in 2015 alone, there were an estimated 212 million new cases of malaria associated with 429,000 deaths. Individuals living in sub-Saharan Africa account for 90% of that disease burden [1]. Over the last decade, disease trends indicate a 20% decline in malaria incidence and a 30% decline in mortality due to efforts that focus on different aspects of the problem, such as providing insecticide-treated mosquito nets, indoor residual spraying, improved rapid diagnostic testing, improved access to effective treatments, and targeted treatment during pregnancy [1]. Unfortunately, limited resources and unstable health systems in sub-Saharan Africa have limited successful interventions in the areas most burdened by the disease. Fewer than half of the 91 affected countries are expected to meet the 2020 milestone of a 40% reduction in case incidence and mortality from malaria [1] (Fig. 34.1).

## 34.2 Abbreviations/Definitions

**WHO** – World Health Organization
**CDC** – US Centers for Disease Control and Prevention
**RDT** – Rapid diagnostic test
**PCR** – Polymerase chain reaction
**G6PD** – Glucose-6-phosphate dehydrogenase deficiency

## 34.3 Basic Concepts

### 34.3.1 The life Cycle of *Plasmodium* Species

Five *Plasmodium* species are known to cause malaria in humans: *Plasmodium falciparum*, *P. malariae*, *P. ovale*, *P. vivax*, and *P. knowlesi*. *P. falciparum* causes the most severe disease and is responsible for most fatal infections. *P. falciparum* is widespread throughout Africa. Malaria

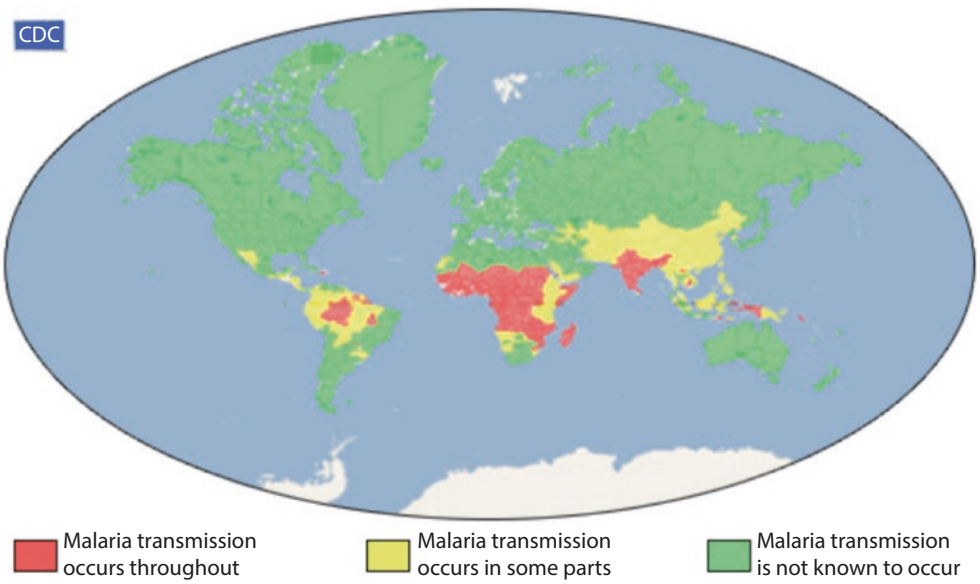
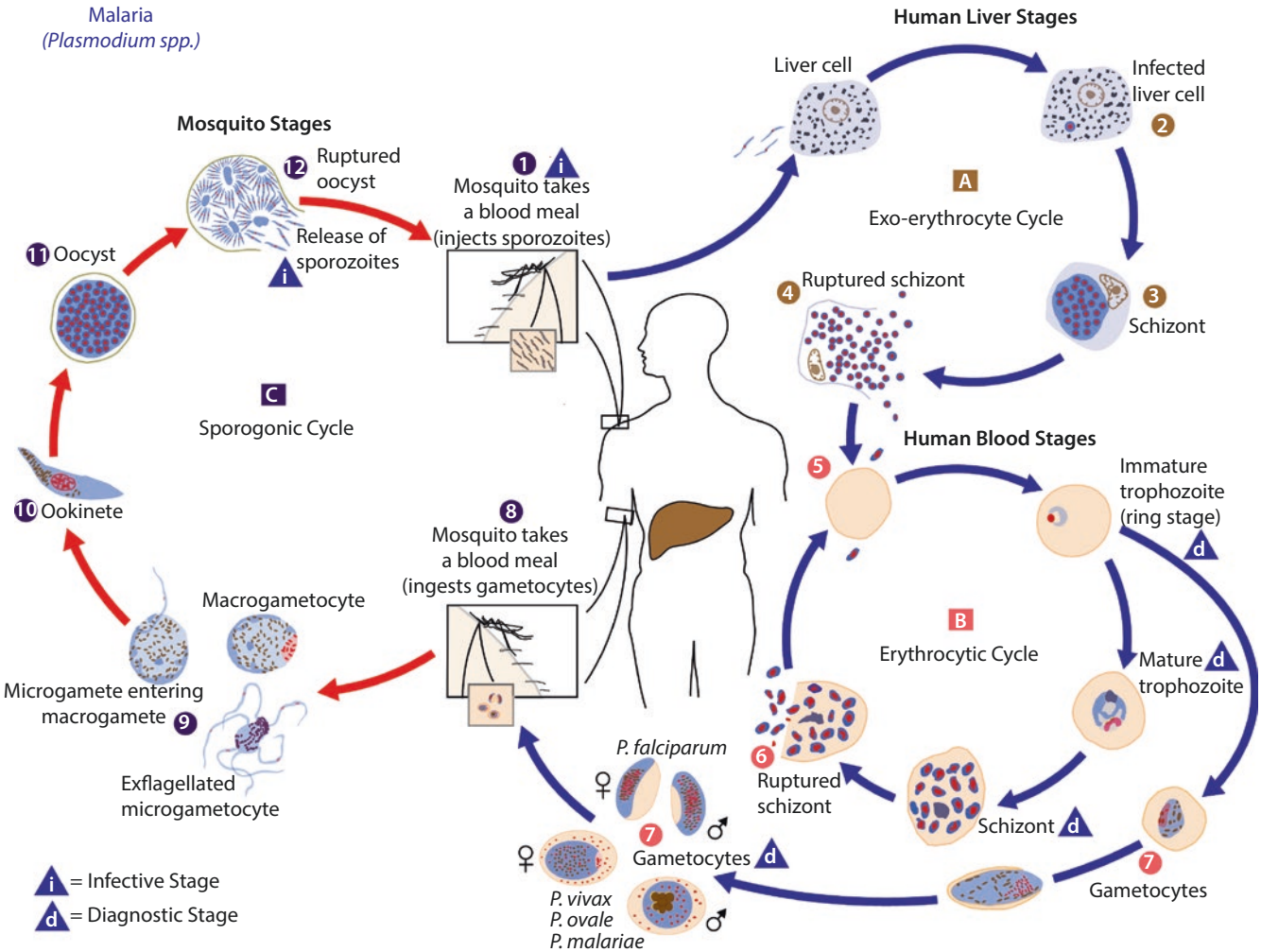



**Fig. 34.1** Global map showing areas where malaria transmission occurs, reprinted from ► https://www.cdc.gov/malaria/about/distribution.html. The map found at the link is interactive and regularly updated by the CDC. Current assessments of malaria activity and recommendations for medications to use for malaria prophylaxis during travel to each country are provided. (Image reprinted with approval from the US Centers for Disease Control and Prevention)

caused by non-*falciparum Plasmodium* species also causes significant morbidity, primarily related to disease-associated anemia and splenomegaly.

*Plasmodium* species infect two hosts, humans and female *Anopheles* species mosquitos. The parasite first multiplies in human hepatocytes, where it does not cause symptomatic disease. Next, asexual forms called merozoites grow and develop inside circulating blood erythrocytes (red blood cells), destroying them. During this period, the patient develops symptoms of disease. The sexual stages of the parasite, called gametocytes, are taken up by the female *Anopheles* mosquito when she bites (see ▶ Chap. 35, ◘ Fig. 35.1). The gametocytes invade, mate, and release asexual sporozoites. Sporozoites are transmitted to a human during the mosquito vector's next blood meal where they enter the bloodstream of the human host and travel to the liver to infect hepatocytes completing the cycle (◘ Fig. 34.2).




◘ **Fig. 34.2** The malaria parasite life cycle involves two hosts. During a blood meal, a malaria-infected female *Anopheles* mosquito inoculates sporozoites into the human host ❶. Sporozoites infect liver cells and ❷ mature into schizonts ❸, which rupture and release merozoites ❹. (Of note, in *P. vivax* and *P. ovale*, a dormant stage [hypnozoites] can persist in the liver and cause relapses by invading the bloodstream weeks or even years later.) After this initial replication in the liver (exoerythrocytic schizogony A), the parasites undergo asexual multiplication in the erythrocytes (erythrocytic schizogony B). Merozoites infect red blood cells ❺. The ring stage trophozoites mature into schizonts, which rupture releasing merozoites. Some parasites differentiate into sexual erythrocytic stages (gametocytes) ❼. Blood stage parasites are responsible for the clinical manifestations of the disease. The gametocytes, male (microgametocytes) and female (macrogametocytes), are ingested by an *Anopheles* mosquito during a blood meal ❽. The parasites' multiplication in the mosquito is known as the sporogonic cycle C. While in the mosquito's stomach, the microgametes penetrate the macrogametes generating zygotes ❾. The zygotes in turn become motile and elongated (ookinetes) ❿ which invade the midgut wall of the mosquito where they develop into oocysts ⓫. The oocysts grow, rupture, and release sporozoites ⓬, which make their way to the mosquito's salivary glands. Inoculation of the sporozoites ❶ into a new human host perpetuates the malaria life cycle. (Image reprinted from ▶ https://www.cdc.gov/malaria/about/biology/index.html. PHIL image 3405, CDC – DPDx/ Alexander J. da Silva, PhD, Melanie Moser)

### 34.3.2 Clinical Presentation of Malaria

After a person is bitten by an infected *Anopheles* mosquito, and infected with *Plasmodium*, a period of 7–30 days may pass before symptoms arise from *P. falciparum*, and weeks to months may pass before symptoms arise from *P. vivax* and *P. ovale* [2–5]. A history of prior treatment for malaria or medication adherence for malaria prophylaxis during a period of risk should not remove malaria from consideration during the evaluation of a patient's illness. Failed treatment may occur if a prior treatment regimen was incomplete, or the parasite was resistant to the chosen therapy. Similarly, failed prophylaxis may occur if the patient did not take the medication as prescribed, was not given proper instructions on when to start and when to stop taking it, or was exposed to and infected with *Plasmodium* resistant to the medication they were taking. Malaria should remain on the differential diagnosis whenever a patient presents with unexplained fever and a history of residing in or traveling to an endemic area any time during the preceding 12 months.

In addition to fever, other non-specific symptoms seen in patients with malaria may include headache, chills, malaise, arthralgia, myalgia, nausea, or vomiting. Clinical signs that may be present include pallor, tachycardia, and splenomegaly. Patients may report cyclical fluctuations in fever occurring every 48–72 h. The periods of fever correlate with the synchronized rupture of infected erythrocytes as merozoites are released into the bloodstream [6].

Severe malaria is caused by *P. falciparum*. Some individuals, including those who are infected for the first time, develop very high grades of parasitemia that result in severe anemia secondary to the extensive destruction of red blood cells. *P. falciparum* also damages small capillaries leading to impaired perfusion of the involved tissues. When the microvascular damage is extensive, the result can be multi-system organ failure. Cerebral malaria is one of the most feared manifestations of severe disease. Patients with cerebral disease have altered levels of consciousness that may progress to coma and death over a very short period of time. The severe central nervous system insult is also, not surprisingly, associated with seizures that can be very challenging to control medically. Other manifestations of severe malaria are also life-threatening. Severe anemia can develop abruptly, impairing oxygen carrying capacity and causing high-output cardiac failure and impairing the oxygenation and perfusion of every organ system. Acute renal failure is also seen regularly with severe disease, typically together with evidence for impairment or failure of other major organs. The development of acute respiratory distress syndrome, coagulopathy, hypoglycemia, or metabolic acidosis portends a poor prognosis. Severe malaria is a medical emergency that requires stabilization and immediate treatment with parenteral antimalarial medication.

### 34.3.3 Host Factors and Disease Severity

Populations that are known to be at high risk for developing severe malaria include pregnant women, children 3 years of age and younger, individuals who are infected with human immune deficiency virus, and travelers who are from non-endemic areas of the world who have not had any prior exposure to *Plasmodium*. Infants less than 6 months of age benefit from the presence of passive humoral immunity from transplacentally acquired maternal antibody to offer partial or complete protection from disease. After 6 months of age, maternal antibody has waned sufficiently that it no longer offers any measurable degree of protection. Exposed infants and young children will develop malaria, and their first infection is almost always associated with the most severe symptoms. The morbidity and mortality associated with malaria are highest in this age group. Older children and adults who have been living an endemic areas have partial or complete immunity to disease as a consequence of prior infection(s), although severe disease can manifest at any age particularly among those with comorbidities.

The observation that groups of black Africans appeared to possess a substantial level of intrinsic resistance to malaria was first appreciated during the 1920s, but an explanation for the observation remained unknown for several decades. It is now well established that four genetic conditions, two affecting hemoglobin; one affecting the activity of the red blood cell enzyme, glucose-6-phosphate dehydrogenase (G6PD); and one affecting the expression of the erythrocyte membrane protein CD234, also known as the Duffy antigen/chemokine receptor (DACR), offer clear biologic advantages in the face of malaria. Individuals with sickle cell trait are heterozygous for the gene encoding the hemoglobin beta chain. One allele is normal; the other encodes sickle hemoglobin (HbS). The presence of sickle cell trait is 50% protective against clinical malaria and 75% protective against malaria that is serious enough to require hospitalization and nearly completely protective against severe illness and death. Similar levels of protection are also well described for individuals with beta thalassemia trait. Glucose-6-phosphate dehydrogenase (G6PD) deficiency is an X-linked recessive disorder of erythrocytes that affects 400 million individuals globally. Enzyme-deficient individuals with malaria develop only mild to moderate illness; lethal infection is exceptionally rare. The protection from severe and lethal infection is explained in part by the inability for *Plasmodium* species to replicate efficiently in the absence of erythrocyte G6PD. The lack of erythrocyte surface expression of DARC is also associated with some clinical protection from malaria. DARC serves as the erythrocyte surface receptor for *P. vivax* and *P. knowlesi*. The erythrocytes of DARC-negative individuals resist invasion by merozoites, but not completely; some cells do succumb to infection. The clinically mild *P. vivax* infections reported in Duffy-negative individuals are best explained by the inability of the parasite to rapidly and efficiently replicate in large enough numbers to lead to moderate or severe illness [2–5].

### 34.3.4 Diagnostic Testing for Malaria

Accurate and timely diagnosis of malaria improves clinical outcomes, especially with *P. falciparum* infection. An accurate

diagnosis of the infecting *Plasmodium* species, and/or the detection of simultaneous infection with more than one species is important because optimal malaria treatment varies depending on the species identified. For example, recommended treatments for *P. ovale* and *P. vivax* infections will eliminate the hypnozoite stages from the liver. In contrast, hypnozoites are not produced during the life cycle of *P. falciparum*.

The gold standard for the diagnosis of malaria is the identification of the parasite on Giemsa-stained blood smears collected from the patient. Both thick and thin smears are prepared, fixed, and stained. Under light microscopy, the thick smear is used to identify the presence of plasmodia, even when present in very low numbers. The thin smear allows more accurate inspection of the parasite forms and the erythrocyte morphology [7]. Both are helpful in determining the species of *Plasmodium* that is present. The thin smear also allows an accurate determination of the parasite burden, reported as the percentage of infected erythrocytes. Higher percentages correlate fairly well with illness severity and allow for an objective measurement of the response to treatment over time.

The diagnosis of malaria using light microscopy requires some basic laboratory supplies and a trained eye, but the testing is inexpensive, not time consuming or technically complex, and offers rapid results. The sensitivity of this test depends on the quality of the reagents used, the quality of the blood smears, and the experience of the laboratory technician [7]. Three separate sets of blood smears, obtained 12–24 h apart, should be examined before a patient is determined to test negative for malaria [2–5]. A final caveat to the interpretation of blood smears is important to appreciate. Identifying plasmodia in a blood smear does not necessarily mean that the patient has a symptomatic infection because the test itself does not distinguish between asymptomatic parasitemia and symptomatic malaria. It is not unusual for individuals who have lived in malarious areas for many years to be parasitemic without any evidence of illness. Clinical judgment is important in deciding whether the patient's illness is explained by the positive blood smear or if other causes for the patient's symptoms should be explored.

Rapid diagnostic tests (RDTs) have also been developed to facilitate diagnosis in the field and in locations where a trained, experienced microscope is not routinely available. RDTs are designed to detect malarial antigens in peripheral blood at the point of care without the need of a microscope of other laboratory equipment. Most antigen-based tests target either the histidine-rich protein II (HRP II) antigen specific to *P. falciparum*, *Plasmodium* lactate dehydrogenase (pLDH), an enzyme that distinguishes *P. falciparum* from *P. vivax*, or malarial aldolase, an enzyme that is common to all *Plasmodium* species. The HRP II test is quite sensitive at detecting low levels of *P. falciparum* antigen making it a very good confirmatory test in non-endemic regions. The assay is, however, of limited clinical utility in endemic regions because antigenemia may persist for months after an infection is treated. Thus, when available, it is recommended that positive HRP II test results be confirmed using light microscopy [2–5]. Antigen-based tests, like blood smears, can be performed on very small volumes of blood obtained by finger-stick sampling.

Serologic tests are more expensive and have no role in diagnosis since results are not available for at least several days. *Plasmodium*-specific antibodies can first be detected approximately 1–2 weeks after the first infection. After that, individuals can remain seropositive for many years with anamnestic responses during each episode of parasitemia.

Polymerase chain reaction (PCR)-based tests are also available and are currently the most sensitive assays available for detecting low-level parasitemia. PCR is, however, more expensive than blood smears or antigen-based tests and requires sophisticated laboratory equipment (although this is changing rapidly), and results are not typically available in a time frame that is realistic to impact decisions about clinical care.

## Case Study

### Practical Examples

**Case 1**

A 2-year-old boy presents to the emergency department (ED) with fever. The family is originally from the Democratic Republic of the Congo but spent 10 years in a refugee camp in Rwanda until resettling in the United States 2 weeks ago. The boy's mother reports that he began to experience fevers and chills two nights ago. He had been eating well until this morning when he declined food and drink and began crying on and off, as if in pain. He has not had any congestion, cough, vomiting, hematuria, diarrhea, or skin changes. He has not received any treatment for this illness other than a cool bath in the evening at the time of the fevers.

His mother reports that she was treated once for malaria during her pregnancy. She carried the pregnancy to term and delivered vaginally without complication. While living in the refugee camp in Rwanda, the boy's mother reports that he was healthy. One week prior to leaving Rwanda, the mother was provided with two medications and instructed to give them to her son to "treat parasites"; she provides documentation listing the medications as artemether-lumefantrine and albendazole. A review of medical records shows that the boy has received all age-appropriate immunizations except for hepatitis A and influenza vaccines that were not available.

**The boy's physical examination shows:**

**Vital signs** – temperature 40.5 °C axillary, heart rate 130 beats per minute, respiratory rate 32 breaths per minute, and blood pressure 90/50. He weighs 13 kg.

**General** – appears stated age, lethargic, but arousable during the examination. His lips are dry; tears are noted.

**Eyes, nose, and throat** – conjunctivae with mild pallor, nares clear without drainage, tympanic membranes clear bilaterally; oropharynx is normal.

**Lymphatics** – no cervical, axillary, or inguinal lymphadenopathy.

**Cardiovascular** – normal heart sounds, tachycardic, regular rate, II/VI systolic murmur heard best at the left sternal border

**Lungs** – mildly tachypneic but not distressed, clear breath sounds bilaterally.

**Abdomen** – soft, non-tender, non-distended, normal liver; spleen tip is palpable 1 cm below left costal margin.
**Gentitalia** – normal circumcised male.
**Skin** – no rashes.
**Neurologic** – lethargic but arousable, will stand but does not want to walk, no focal deficits elicited on cranial nerve or motor examinations, coordination assessment limited due to limited cooperation; reflexes are normal.

A dose of oral acetaminophen is given in the office. Thirty minutes later his axillary temperature is 38.4 °C. The remainder of his physical examination is unchanged.

**Differential Diagnosis**

Fever with localizing signs is very common in young children. In the United States, the majority of these children have self-limiting viral illnesses. Influenza, roseola (HHV-6), adenovirus, and Epstein-Barr virus (EBV) are just a few of the many possibilities. Although each of these viral infections may have related symptoms, such as cough (influenza), rash (roseola), conjunctivitis (adenovirus), or pharyngitis (EBV), high fever alone is not atypical for any of them in this age group. Less frequently, young children in the United States with fevers without localizing signs may have common bacterial infections that are not immediately obvious, such as a urinary tract infection, pneumonia, or occult bacteremia. A minority of febrile children will be found to have less common bacterial infections such as an osteoarticular infection or meningitis. The presence of splenomegaly, as described in the boy from the vignette, is non-specific but does broaden the differential diagnosis in the case described because the patient lived in a part of the world endemic for infectious diseases that are not seen very often in the United States. Vector-borne infections such as malaria, dengue, chikungunya, and trypanosomiasis should be included in differential diagnosis for the boy under consideration after learning that he was born in and lived in Rwanda until 2 weeks ago. Life in close living quarters of a refugee camp also increases the risk for communicable disease from food- and water-borne infections like salmonellosis and hepatitis A and E to airborne infections like tuberculosis. Salmonellosis most typically causes diarrhea, but salmonella enteric fever can present with high fever alone. Similarly, infection with hepatitis A virus typically causes impressive elevation of serum hepatic transaminases and hyperbilirubinemia in adolescents and adults leading to the obvious physical examination finding of jaundice, but young children infected with hepatitis A virus are almost always anicteric (tuberculosis).

Documentation that the boy was treated with the antimalarial medication, artemether-lumefantrine, immediately prior to leaving Rwanda seems to make the diagnosis of malaria unlikely until further discussion with the boy's mother reveals that she gave him one dose, but the pills were bitter, so he refused to take them.

**Diagnostic Evaluation**

A few basic diagnostic studies should be done prior to launching a more comprehensive investigation for all of the possibilities listed in the differential diagnosis above. A blood and urine culture should be obtained. Clues about more likely diagnoses may become evident from results of a complete blood count and chemistries, including serum hepatic transaminases. Thick and thin blood smears may reveal the underlying diagnosis within a few hours if blood parasites such as plasmodia or trypanosome are seen.

A few minutes later, the boy's mother calls for the physician to return to the room because her son is becoming very difficult to arouse. As the provider enters the room, the patient's eyes roll back, his legs stiffen, and he has a tonic clonic seizure of his upper extremities that lasts 30 s. The differential diagnosis now needs to be revised to include acute life-threatening neurologic conditions involving fever and seizures. Considerations should now also include meningitis, meningoencephalitis, and cerebral malaria. As the provider is preparing to perform a lumbar puncture, he receives a call from the laboratory supervisor who informs him verbally of critical test results including a blood hemoglobin of 5 g/dL and the presence of *P. falciparum* species seen in approximately 30% of erythrocytes on blood smear (◘ Fig. 34.3).

A diagnosis of cerebral malaria, caused by *P. falciparum*, is made. Plans to perform the lumbar puncture are abandoned, and intravenous quinidine and clindamycin are requested from the hospital pharmacy. Arrangements are made to admit the boy to intensive care unit care for neurologic and cardiac monitoring. Intravenous antimalarial treatment is necessary until he becomes clinically stable and can complete a 3-day oral course of artemether-lumefantrine or atovaquone-proguanil.

**Case 2**

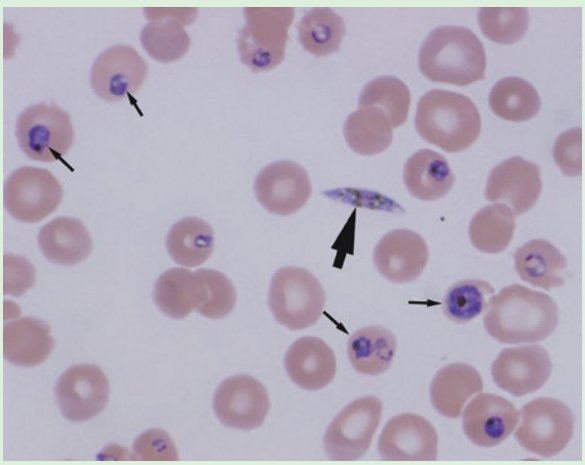
A 38-year-old man presents with 2 days of fever to 40 °C, chills, body aches, and headaches. He denies rhinorrhea, congestion, cough, rash, joint swelling, nausea or vomiting, dysuria, hematuria, diarrhea, or change in stools from baseline. He has no significant past medical or surgical history. His only current medication is atovaquone-proguanil. The patient is a law professor who just returned from his first trip to southern India, where he spent the past 6 weeks teaching an international human rights course in collaboration with a local university. The atovaquone-proguanil was prescribed for malaria prophylaxis during that assignment. He reports using the medication as instructed and explains the he took it daily, starting 2 days before arriving to India and continuing for 7 days after his return. He took his last dose this morning.

He avoided "street foods" during his travel, preferring to prepare his own meals. He explains that he was careful to use bottled water for drinking and was diligent with food preparation.

**Physical Examination**

Vital signs are normal except for a temperature of 38.9 °C orally.

His physical examination is normal.



◘ **Fig. 34.3** Shown is the Giemsa-stained thin blood smear with high-grade *P. falciparum* parasitemia, estimated at 30%. Several developmental forms of the malaria parasite are seen inside the infected erythrocytes (small arrows). The large arrow identifies a large, banana-shaped, extracellular gametocyte. *P. falciparum* is the only *Plasmodium* species with banana- or crescent-shaped gametocytes; the gametocytes of the other species are morphologically round. (Image provided by Dr. Scott Ridell)

**Differential Diagnosis**

Fever in a returning traveler always opens the possibilities to a range of new, sometimes unusual, exposures at the destination or during the journey. Keep in mind that common infections are common, and every differential diagnosis should be developed by considering the most common possibilities first. The law professor's travel history is interesting and unusual but should *not* distract the provider from starting with a differential diagnosis of usual illnesses that can occur without that travel history. Details related to the travel can then be used to expand the list. The man's illness, fever without localizing signs, is consistent with a viral syndrome. He has no past medical history or underlying chronic illness to place him at higher risk for a bacterial infection, but his recent travel to India does broaden the differential diagnosis to include infections endemic to the region such as malaria, typhoid, dengue, chikungunya, and scrub typhus.

**Diagnostic Evaluation**

In this adult patient with fever and no localizing signs, and recent travel to India, the initial laboratory evaluation should include blood cultures, a complete blood count, serum chemistries including hepatic transaminases, and thick and thin blood smears. Without skin findings (rash or eschar), scrub typhus is unlikely, but serologic testing can be performed by measuring antibody titers to *Orientia tsutsugamushi*, if desired. His blood is drawn and sent to the laboratory for testing. Since he appears well, and as a normal physical examination except for fever, the provider advises him to return home, to use acetaminophen to help control the fevers, to drink plenty of fluids, and to get some rest rather than waiting in the office for the test results.

Later the same day, a technician working in the clinical microbiology laboratory contacts the provider with news that the malaria blood smear is positive but that the *Plasmodium* species identification won't be available until the next day. As a visitor to a malaria-endemic area, the patient is at risk for severe disease because he has no prior immunity or exposure to malaria; infection with *P. falciparum* is, however, much less common in India than in Africa. The provider contacts the patient to inform him that he has malaria and asks him if he has had any changes in his symptoms. He confirms that his symptoms are the same as they were earlier in the day. The patient is informed that treatment for the infection will be prescribed the next day, once the species of the malaria parasite is known. The next morning, the microbiologist confirms that the patient's thin blood smear is positive for *P. vivax*, with fewer than 1% of the erythrocytes infected (Fig. 34.4). The provider considers the treatment options for his patient. Chloroquine-resistant *P. vivax* is prevalent in India, so it cannot be used. Atovaquone-proguanil is not likely to work since he was taking it for prophylaxis when he acquired the infection. Under these circumstances, the recommended therapy is a 3-day course of artemether-lumefantrine. The life cycle of *P. vivax* (and *P. ovale*), unlike that of *P. falciparum*, includes the generation of liver hypnozoites, a parasite form that lies dormant in hepatocytes with potential to cause disease recurrence. Artemether-lumefantrine does not eradicate hypnozoite forms, so a second medication must also be prescribed to reduce the risk of relapse. The antimalarial drug of choice to treat hypnozoite forms is primaquine. Primaquine should be taken for 14 days. It is generally well tolerated but should only be prescribed after confirming that the patient does not have G6PD deficiency because enzyme-deficient patients are especially prone to develop primaquine-induced red blood cell hemolysis. The law professor G6PD testing is normal, and his fevers resolve after the 3-day course of artemether-lumefantrine. He completes a 14-day course of primaquine as prescribed and is counseled regarding the potential for relapse of symptoms during the next 6–12 months.

**Case 3**

A 17-year-old female presents to an urgent care facility with complaints of fever. She recounts that during the past 2 weeks, she's

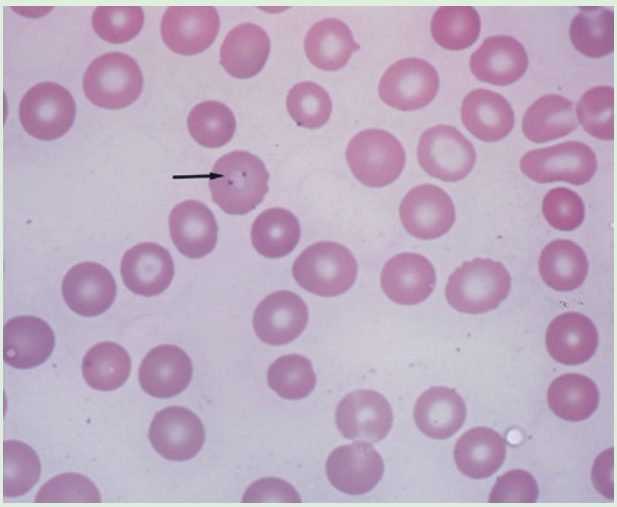


**Fig. 34.4** Shown is the Giemsa-stained thin blood smear with low-grade *P. vivax* parasitemia. Inspection of dozens of high-power fields was necessary to identify the species as *P. vivax* with confidence because of the extensive morphologic similarities to *P. ovale*. Only one of the erythrocytes in this high-power field is infected. Note that the infected cell is approximately 1.5 times the size of the neighboring, uninfected cells. This finding is characteristic for *P. vivax* and *P. ovale*, but not *P. falciparum*. (Image provided by Dr. Scott Ridell)

woken from sleep with fever, shaking chills, and night sweats on four separate occasions. She also describes generalized malaise and fatigue during this time, causing her to sit out from soccer practice because of a lack of energy. She complains of a headache and body aches when the fevers spike. She denies any rhinorrhea, congestion, cough, rash, joint swelling, nausea or vomiting, dysuria, hematuria, diarrhea, or change in stools from baseline. The only medication she takes is ibuprofen.

This patient was born in Malaysia and lived in Indonesia for 5 years before immigrating to the USA 9 months ago on a student visa. She is staying with a host family locally and attending a charter school. She denies any history of medical problems in the past. She has never been sexually active.

Healthcare providers have seen her twice during the past 9 months. On both occasions, she was told she had a "viral syndrome." She was instructed to take ibuprofen for the fevers. No laboratory testing was performed during either of the prior illnesses. After the second episode of fever, the patient took a 3-day course of artemether-lumefantrine that she had packed from home, at the insistence of her mother in Indonesia.

**Physical Examination**

**Vital signs** – temp, 37.6 °C axillary, HR 80, RR 18, BP 98/68.
**General** – comfortable, well appearing, in NAD.
**Head** – no conjunctival pallor or icterus, normal nares and oropharynx, tympanic membranes clear bilaterally.
**Lymph** – no cervical, axillary, inguinal lymphadenopathy.
**Cardiac** – normal heart sounds, no murmurs.
**Lungs** – clear lung sounds bilaterally.
**Abdomen** – soft, non-tender, non-distended, normal liver; spleen is palpable 5 cm below left costal margin and is not tender.
**Skin** – no rashes.
**Neurologic** – normal.

**Differential Diagnosis**

The differential diagnosis for an adolescent female presenting with episodic fevers, chills, night sweats, and fatigue for 2 weeks and who has significant splenomegaly on physical examination is, again, rather broad. It is important to consider common general causes of her symptom complex first and then expand the differential diagnosis based on her social history. In this case, the differential diagnosis includes a number of acute infections, but, in general, it seems illogical that the risk or exposure for the vast majority of infections would be related to living in Indonesia since she has lived in the USA for 9 months. The incubation period for nearly all infectious diseases is much shorter than that!

The differential diagnosis also includes few diseases that are not infections. Hematologic malignances, particularly non-Hodgkin's lymphoma, can present with fever and splenomegaly. Two of the most common physical examination findings in patients with hemophagocytic lymphohistiocytosis (HLH) are also fever and splenomegaly. HLH is a life-threatening, immune-mediated inflammatory condition that can be familial or can be triggered by an underlying infection. The patient's report that she has had two similar prior illnesses may also be an important clue.

Infections that cause fever and splenomegaly include infectious mononucleosis secondary to either Epstein-Barr virus (EBV) or cytomegalovirus (CMV). Typhoid and enteric fever may also present this way. Fever and splenomegaly are also commonly seen with subacute bacterial endocarditis, but not usually to the exclusion of other manifestations. Bacterial abscesses of the spleen are uncommon but worth considering in the comprehensive differential diagnosis either from hematogenous seeding during transient bacteremia (typical for *Staphylococcus aureus* or *Salmonella* species) or as a complication from mitral or aortic valve endocarditis. Left-sided endocarditis would be expected, however, to be associated with a heart murmur and other signs of embolic disease or metastatic infection.

Three infectious diseases that are found in Indonesia; can present with fever, chills, night sweats, and splenomegaly; and can first manifest symptoms 9 months later (or longer!) include malaria, tuberculosis, and brucellosis. Of these three, malaria is the only one that would explain all three of her episodes of similar illness, if indeed they were all caused by the same underlying problem.

All five *Plasmodium* species known to infect humans, *P. falciparum*, *P. malariae*, *P. ovale*, *P. vivax*, and *P. knowlesi*, are circulating in Indonesia. The patient has had malaria in the past, and she traveled to the USA with artemether-lumefantrine, perhaps not fully understanding that infections caused by *P. ovale* and *P. vivax* require a second medication to reduce or eliminate hypnozoites from the liver. A relapse of malaria caused by one of these two species seems to be the most likely diagnosis.

**Diagnostic Evaluation**

This adolescent patient with fever, chills, night sweats, and splenomegaly who lived in Indonesia until 3 months ago would benefit from an initial laboratory evaluation that includes blood cultures, a complete blood count, serum chemistries including hepatic transaminases, thick and thin blood smears, and serologic testing for cytomegalovirus and Epstein-Barr virus infection. Ultrasonography of the abdomen should also be considered, in part to rule out the unlikely diagnosis of a splenic abscess but, more importantly, to determine whether the one abnormal physical examination, splenomegaly, is associated with other intra-abdominal pathology such as lymphadenopathy.

Review of the patient's laboratory results reveals mild thrombocytopenia, a normal blood hemoglobin concentration, hematocrit, and total white blood cell count. The IgM and IgG antibodies for both cytomegalovirus and Epstein-Barr virus are negative. The blood cultures show no growth. The first thick blood smear is negative for malaria. The abdominal ultrasound reveals a normal liver and a markedly enlarged spleen with a normal, homogeneous echotexture.

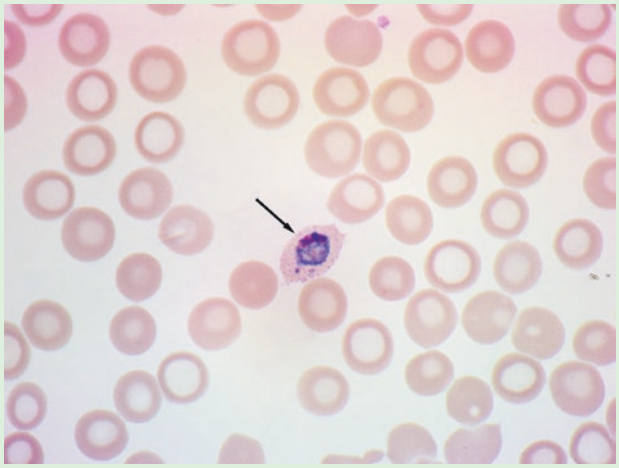


**Fig. 34.5** Shown is the Giemsa-stained thin blood smear from a patient with low-grade *P. ovale* parasitemia. Morphologically, it may be impossible to distinguish between *P. ovale* and *P. vivax*, especially when only a few parasite forms are seen. Note the oval shape of the single infected erythrocyte in this high-power field (arrow). The species name comes from the observation that 20% of cells infected with *P. ovale* assume an oval shape. The finding of fimbriated erythrocytes is non-specific but is common with *P. ovale* and *P. vivax* infection. (*Image provided by Dr. Scott Ridell*)

Understanding the limitations of a single blood smear for the diagnosis of malaria, especially when the patient is without fever, two additional smears are collected approximately 12 h apart. No malaria forms are seen. The local laboratory does not perform antigen- or PCR-based testing. The clinical suspicion remains high that the patient's episodic fevers and splenomegaly are due to malaria. The features of her illness are consistent with a diagnosis of hyperreactive malarial splenomegaly. The CDC is consulted and recommends that a blood sample be sent to the state reference laboratory for PCR-based testing.

In the week that follows, the teen has no additional fevers and notices improvement in her energy level. She states that the same thing happened following both of her prior febrile illnesses. The PCR test performed at the reference laboratory is positive for *P. ovale* illustrating the improved sensitivity of PCR-based testing over blood smear analysis even when multiple smears are collected at 12-h intervals.

For illustration purposes, a peripheral blood smear that is positive for the presence of *P. ovale* is shown in Fig. 34.5.

The patient's febrile illness and both of her prior febrile illnesses are consistent with relapses of malaria caused by emerging liver *Plasmodium* hypnozoites. Chronic infection with *P. ovale* (or *P. vivax*) is not always associated with a significant anemia. Moderate to massive splenomegaly, however, is quite typical. Her mild thrombocytopenia is best explained by "hypersplenism" or splenic overactivity leading to sequestration of platelets. Mild to moderate anemia secondary to the uptake and elimination of erythrocytes before they are senescent (defined as more than 120 days in circulation) can also be seen with hypersplenism.

Patients with splenomegaly or hypersplenism and parasitemia detected by blood smear, antigen testing, or PCR-based assay should be treated with chloroquine, atovaquone-proguanil, or artemether-lumefantrine for 3 days. Chloroquine is prescribed. The patient is also counseled about the importance of treatment for hypnozoite forms of *P. ovale*. After confirming that she is not G6PD deficient, she is prescribed a 14-day course of primaquine. During a follow-up visit 3 months later, the patient reports that her energy is back to normal and that she has had no further episodes of fever or chills. Repeat blood testing shows resolution of her mild thrombocytopenia, and a repeat abdominal ultrasound confirms that her splenomegaly has resolved.

## 34.4 Key Points

### Case 1: Key Points

- Fever without localizing signs has a broad differential diagnosis. A history of living in or traveling to areas endemic to certain diseases can expand that list even further.
- Common infections are common. A differential diagnosis should be developed by considering the most common possibilities first and then be expanded and/or refined based on clues provided by the history (e.g., living in a refugee camp on Rwanda), physical examination (e.g., splenomegaly), laboratory results (e.g., severe anemia), and evolving clinical course (e.g., seizures).
- The recognition of signs and symptoms of severe malaria requires prompt intervention to avoid fatal complications.
- A history of prior "treatment" for malaria may be reassuring, but remember to consider reasons why treatment may fail or appear to fail such as patient non-adherence, unreliable medication sources, malarial drug resistance, and the risk for reinfection or relapse.

### Case 2: Key Points

- Malaria prophylaxis reduces, but does not eliminate, the risk of developing disease during or after travel to endemic areas
- Malaria should not be treated with the same medication that failed when used for prophylaxis
- Treatment to eliminate hepatic hypnozoite forms that are produced by non-*falciparum* malaria species is necessary to reduce the frequency of disease relapse
- Patients who require treatment with primaquine should be screened for G6PD deficiency before being prescribed the medication

### Case 3: Key Points

- Always inquire where a patient is *from*, but also where they have *been*, and when they were there to best establish the most appropriate timeline for potential travel-related disease exposures. Travel history is important.
- When test results fail to confirm a solid clinical diagnosis, alternative illnesses should certainly be considered and explored. In addition, revisit the earlier thinking and the path of deductive reasoning used to come to the initial clinical diagnosis, and review any limitations of the diagnostic tests that were performed. If that diagnosis still seems valid and likely, do not hesitate to consult with expert authorities such as those working at CDC or to reevaluate with more sensitive or alternative diagnostics, if available.

## 34.5 Summary

Malaria causes substantial morbidity and mortality across the globe. Five different *Plasmodium* species are known to cause malaria in humans. Individuals with malaria develop fevers, often associated other non-specific complaints such as malaise, headache, and myalgias. On physical examination, signs associated with anemia may be appreciated such as resting tachycardia, or pallor. Splenomegaly is common. Severe *P. falciparum* infection includes life-threatening manifestations of the disease such as profound anemia, cerebral malaria, acute respiratory distress syndrome, coagulopathy, acute renal failure, hypoglycemia, and acidosis. Severe disease and mortality associated with severe malaria are most common in young children and pregnant women. Infections caused by *P. vivax* and *P. ovale* include the generation of liver hypnozoites, dormant forms of the parasite that reside in hepatocytes. Hypnozoites can emerge to cause recurrent disease months or years after the initial infection explaining how some people who no longer live or travel to endemic area of the world appear to development malaria without recent exposures to the mosquito vector. Inspection of Giemsa-stained thick and thin blood smears by light microscopy remains the most commonly used diagnostic test to detect parasitemia. Antigen-based testing has emerged as a sensitive diagnostic that requires less technical skill and minimal laboratory supplies lending its utility to point of testing in the field or in areas where experienced microscopists are not available to read blood smears. PCR-based testing is also emerging but remains expensive and requires sophisticated instrumentation and a higher level of technical expertise. Its current major advantage is that it is much more sensitive for the diagnosis of low-grade parasitemia than other available tests. Efforts to develop single-step PCR-based testing using portable, disposable single-use devices have already been successful for other infectious diseases (e.g., influenza) and may soon emerge as an approved, rapid, highly sensitive, and preferred diagnostic for point of care testing. A variety of antimalarial medications are available to treat malaria; however long-standing (chloroquine) and emerging (all of the others) drug resistance is problematic. Those who treat malaria need to be remember that infections caused by *P. vivax* and *P. ovale* require dual therapy that includes at least a 3-day course of medication to treat parasitemia, followed by 14 days of treatment with primaquine to reduce or eliminate liver hypnozoite forms. Patients for whom primaquine treatment is necessary must be tested for G6PD deficiency before the medication is prescribed. Ongoing efforts to facilitate access to reliable and effective treatments and to improve prevention strategies continue. Recent progress in the development of a safe and effective vaccine appears to offer the promise that 1 day soon, malaria will be added to the growing list of vaccine preventable infections.

## 34.6 Exercises

Please refer to the supplementary information section for answers to these exercises.

1. Which of the following regions of the world has the highest burden of severe *P. falciparum* malaria?
   1. Southeast Asia
   2. South America
   3. Sub-Saharan Africa
   4. The Indian subcontinent
   5. The Middle East

2. Interventions proven to reduce malaria transmission include all of the following EXCEPT:
   1. Insecticide-treated bed nets
   2. Indoor residual spraying
   3. Childhood vaccination
   4. Access to rapid diagnostic tests
   5. Improved distribution of quality medications to high-risk patients

3. Which of the following signs or symptoms is specific for the diagnosis of malaria?
   1. Headache
   2. Myalgias
   3. Splenomegaly
   4. Conjunctival pallor
   5. None of the above

4. Which of the following medications is most effective at reducing or eliminating the dormant hypnozoite forms of *P. ovale* and *P. vivax* from the liver?
   1. Atovaquone-proguanil
   2. Mefloquine
   3. Chloroquine
   4. Primaquine
   5. Doxycycline

5. Which of the following describes an important advantage of using polymerase chain reaction (PCR)-based testing for the diagnosis of malaria?
   1. PCR is relatively inexpensive compared to other available diagnostic tests
   2. PCR distinguishes between asymptomatic parasitemia and symptomatic malaria
   3. PCR is the only available test that detects the presence of *P. malariae*
   4. PCR is more sensitive than direct visualization of parasites on stained blood smears
   5. PCR is more widely available that other test modalities



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# Yellow Fever and Dengue

## Fever, Hepatitis, and Jaundice in a Returning Traveler
## Fever, Retro-Orbital Headache, Generalized Myalgias, Arthralgias and Bone Pain in a Returning Traveler

*Zachary A. Jones and Stephen J. Thomas*




J. Domachowske (ed.), *Introduction to Clinical Infectious Diseases*,
https://doi.org/10.1007/978-3-319-91080-2_35

**Learning Objectives**

- To review the history, pathogenesis, and management of yellow fever and dengue virus infections

## 35.1 Introduction

The *Flavivirus* genus contains over 30 viruses known to cause disease in humans including yellow fever; dengue serotypes 1, 2, 3, and 4; and the highly publicized Zika virus [1]. Many of the viruses included in this genus are spread by arthropod mosquito vectors, including yellow fever, dengue, Zika, West Nile, and Japanese encephalitis viruses [2] (■ Fig. 35.1). While Zika virus emerged as a global health emergency in 2015, yellow fever virus has been an important human pathogen in the Western Hemisphere for more than four centuries, and dengue escalated to the most common vector-borne viral illness in the world during the twentieth century. This chapter will focus on the history, epidemiology, pathogenesis, treatment, and prevention of yellow fever and dengue viruses [▶ Call Out Box 35.1].

**Call Out Box 35.1**

The word *arbovirus* has nothing to do with virus nomenclature or taxonomy. It is a shortened form of stating "arthropod-borne virus." Arthropods are invertebrates with an exoskeleton, a segmented body, and paired joint appendages. Arthropods known to transmit viral, bacterial, or parasitic infections to humans include mosquitos, ticks, sandflies, tsetse flies, *Simulium* black flies, triatomine insects, fleas, and body lice. Of these, arboviral infections are transmitted by mosquitos, ticks, and sandflies.

## 35.2 The History of Yellow Fever

The first recognized case of yellow fever (YF) in the Western Hemisphere was described during an outbreak in the Yucatan in 1648 [3]. Molecular analysis of the virus has since placed the introduction of YF to the Western Hemisphere approximately 300 years ago, likely brought to the area via slave ships from the African continent [4]. At the time, yellow fever was thought to be transmitted by means of miasma (an unhealthy smell or vapor). Once YF established itself in the Western Hemisphere, it spread rapidly throughout port cities of Central and North America. One of the most striking outbreaks in the historical record occurred in Philadelphia in 1793, when YF was reported to kill roughly one tenth of the city's population [5].

During the latter part of the nineteenth century, in response to catastrophic loss of life related to YF infection, the US Army created the US Army Yellow Fever Commission. Major Walter Reed, MD, conducted his seminal research in this area as part of the fourth commission in Havana, Cuba. His investigative efforts helped to establish the practice of written informed consent as part of clinical

■ **Fig. 35.1** Shown are images of a female *Aedes aegypti* (*left*), *Anopheles* species (*middle*), and *Culex* species (*right*) mosquito. *A. aegypti* is the arthropod vector for the transmission of dengue, chikungunya, Zika, and yellow fever viruses. *Anopheles* species transmit malaria and *Culex* species transmit West Nile virus. (Image kindly provided by Froilan Heras)

research [6]. Among the discoveries made by Dr. Reed's team was the postulate that an infectious particle was responsible for YF and that this agent of disease was transmitted by the *Aedes aegypti* mosquito, not through fomites or miasma [7]. Reed and his team confirmed the mosquito transmission hypothesis of Cuban epidemiologist Carlos Finlay. During testing, it was determined that serum remained infectious after microfiltration, essentially ruling out a bacterial cause for YF.

In the decade following Reed and colleagues' publication, the Rockefeller Foundation vowed to eradicate YF despite not yet knowing the causative agent. In 1927, Major Henry Beeuwkes, Adrian Stokes, and others obtained blood from a 28-year-old African man named Asibi who had been diagnosed clinically with YF. Asibi's blood successfully transferred clinical yellow fever infection to a rhesus monkey. Tragically, Adrian Stokes died from YF during the course of those experiments. Shortly after Stokes' death, his team helped to determine that the agent responsible for clinical yellow fever disease was a virus [8]. Max Theiler, and others, attenuated the Asibi strain of YF virus through serial passages in monkeys followed by additional passages in both mouse tissue and chicken embryos. The resulting YF 17D vaccine strain is the same attenuated virus still used globally to prevent yellow fever [9]. In 1951, Theiler received the Nobel Prize in Physiology or Medicine for his role in developing an effective YF vaccine.

## 35.3 The History of Dengue

One of the first comprehensive clinical descriptions of dengue fever in the Western Hemisphere was attributed to Benjamin Rush during a Philadelphia outbreak in 1780 [10]. The word dengue is thought to be derived from the Swahili word dinga, as used in the phrase "ka dinga pepo" meaning cramp-like seizure caused by an evil spirit. The phrase "quebranta huesos" or "that which breaks bones" dates to a Spanish description of a febrile illness from 1771 [11]. Reported outbreaks during this period were common from nearly all subtropical and tropical areas of the Western Hemisphere and all along the East Coast of the United States [12].

Mosquito-borne transmission of dengue was established by Graham in 1903. US Army Captain P. M. Ashburn and Lieutenant Charles Craig built off this work in their dengue transmission studies while stationed in the Philippines during the first decade of the twentieth century. Through their work, they discovered that the particle responsible for dengue was caused by a filterable agent [13]. *Ren Kimura* and *Susumu Hotta* first isolated the dengue virus in 1943, and later Sabin and Hammon established the existence of four distinct serotypes of dengue virus, each capable of causing disease or death [14]. Much of the foundational understanding of dengue transmission and immunology was discovered using experimental human infection.

## 35.4 Epidemiology of Yellow Fever

Yellow fever (YF) is endemic to tropical and subtropical countries in sub-Saharan Africa and South America [15]. Despite the presence of abundant *Aedes aegypti* mosquitos in Asia, where other flaviviruses such as dengue viruses are well established, epidemics of YF have not yet been reported from that region of the world [16]. Globally, an estimated 200,000 cases and 60,000 YF-related deaths occur annually [17]. Estimates may be grossly understated due to failed recognition and widespread under-reporting from many parts of the world. Community-based epidemiologic studies indicate that the true number of new infections may be 10–500 times higher than reported [18]. Worldwide, the majority of YF cases occur in Africa. During a 2016 outbreak in Angola alone, there were 4300 suspected cases and 376 deaths [19].

Transmission of YF is known to occur in two cycles: the urban cycle and the sylvatic or jungle cycle. The urban cycle involves transmission of the virus from the *Aedes aegypti* mosquito to humans with sustained human-mosquito-human transmission thereafter. In the sylvatic cycle, transmission of the virus occurs chiefly between mosquitos and nonhuman primates. As humans enter the jungle area, they are bitten by forest canopy mosquitoes and can act as an incidental hosts in this transmission cycle. The arboreal mosquitos *Haemagogus* spp. and *Sabethes chloropterus* are vectors responsible for the sylvatic cycle in the Western Hemisphere [20]. Yellow fever cases across South America are now thought to be almost exclusive to the sylvatic cycle, as there have been no reported cases of urban acquired infection in Brazil since 1945 [21]. Despite the absence of urban transmission, Brazil experienced its worst YF outbreak in decades during 2017, with more than 1350 suspected cases [22]. Mass vaccination protocols and insecticide disbursement continue in an effort to stave off the human-mosquito-human urban transmission cycle, a problem that would undoubtedly lead to catastrophic morbidity and mortality across the country's heavily populated large cities.

## 35.5 Epidemiology of Dengue

Dengue fever is now endemic to more than 100 countries. Recent estimates indicate that there are 390 million new infections per year with more than 3.5 billion people living in at-risk areas [23, 24]. It is difficult to estimate the total burden of dengue because 80% or more of all cases are self-limiting [23]. In response to infection, the human host develops serotype-specific immunity that provides a very short-lived partial protection across the other serotypes (cross-protection) [25]. *Aedes aegypti* and *A. albopictus* mosquitoes are the primary vectors of dengue. Meta-analyses indicate that the densest areas of incidence occur in climates

with temperatures between 22 ° C and 29 °C, correlating with conditions needed for the *Aedes aegypti* vector to flourish [26].

Post WWII, urbanization led to the spread of industrialized debris in tight urban settings that can serve as reservoirs for free-standing pockets of water. These collections of water serve as highly effective breeding grounds for the *Aedes* mosquito [27]. Eleven countries in Asia have been declared hyperendemic for dengue by the World Health Organization. While more than 75% of worldwide dengue burden is in Asia, more than 2.3 million cases and 1318 deaths were reported in Latin America and the Caribbean during 2013. The global disease burden is enormous [28]. Following YF control initiatives, the *Aedes* mosquito was nearly eradicated from the Caribbean. Globalization and frequent travel across dengue endemic areas have, however, allowed dengue to become reestablished. Dengue incidence data from most of Africa are limited, but it is known that the *Aedes* mosquito vectors are widespread across the continent and the consistent observation of dengue infection in returning travelers indicates there is some level of sustained transmission [25]. Dengue virus is well established in Mexico, but outbreaks in the United States along the Mexico-Texas border are not very common. Most cases of dengue that are reported in the continental United States are seen in travelers returning from endemic areas, although autochthonous cases have recently been reported from the Florida Keys [29]. Locally acquired dengue infection has also been reported from Hawaii [30]. Absent the widespread availability of a highly efficacious dengue vaccine, vector control and personal protective measures remain the primary means of prevention.



## 35.6 Yellow Fever Virus and Viral Pathogenesis

Yellow fever virus is a positive-sense single-stranded RNA virus of the genus *Flavivirus*, family *Flaviviridae* [31]. Seven distinct genotypes have been identified, five in Africa and two in South America [32]. The capsid, pre-membrane, and envelope proteins of YF are structural proteins; the E protein has a significant role in host cell attachment and internalization. Seven nonstructural proteins, NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5, have been described as necessary for successful viral replication [33].

YF virus is transmitted to humans through the bite of an infected female mosquito. The virus appears to first infect the Kupffer cells in the liver and then shortly thereafter infects lymph nodes and bone marrow splenocytes [34]. Plasma studies of healthy recipients of the 17D YF vaccine indicate an increased concentration of serum tumor necrosis factor-α and interleukin-1 receptor antagonist concentrations 2 days after inoculation [35]. Similar increases during infection probably explain the malaise, myalgia, and fevers experienced during the early phase of the illness. After this phase, the virus infects hepatocytes eventually leading to the formation of eosinophilic inclusions known as Councilman bodies. Viral antigen studies of human liver sections at autopsy indicate that the primary mode of cell death is not through necrosis. Instead, tissue damage occurs in a more organized fashion via apoptosis with the creation of Councilman bodies. Stains for viral antigen indicate that the mid-zone of the liver is the area primarily involved [36]. YF virus is also cardiotropic. Infection of cardiac myocytes can lead to myocarditis, cardiogenic shock, and fatal arrhythmias [37]. Intravascular volume depletion can lead to acute renal failure secondary to poor renal perfusion and acute tubular necrosis [38]. The coagulopathy that is characteristic of severe yellow fever infection is related to decreased hepatic synthesis of clotting factors.

## 35.7 Dengue Viruses and Viral Pathogenesis

Four antigenically distinct serotypes of dengue viruses (DENV) are known to cause dengue, serotypes 1, 2, 3, and 4. DENVs are single-strand positive-sense RNA viruses of the genus *Flavivirus*, family *Flaviviridae.* After entering human host cells, DENV RNA is released and translated into three structural and seven nonstructural (NS) proteins, NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5s [39].

The incubation period for illness is 4–10 days following infection by an infected female mosquito. In children, first-time dengue infections are often clinically inapparent or asymptomatic while primary dengue in adults more often results in symptomatic disease. Adults with dengue infection typically complain of fever, retro-orbital headache, eye pain, bone pain, and rash. Since the four dengue serotypes are similar, but antigenically distinct, infection with one serotype does not confer complete protective immunity to the other three. Individuals who have already been infected with one dengue serotype, and who are exposed to a second serotype, have a high likelihood of asymptomatic infection, but these circumstances are somewhat counter-intuitively associated with a 50–100-fold increased risk for life-threatening, severe, hemorrhagic disease [40].

Dengue virus has a broad tropism in vivo. Initially, the virus can only be observed at the site of the bite chiefly in the Langerhans cells of the skin [41]. Viremia is present in the human host for 4–6 days, the time period when the patient is febrile and most symptomatic. Viremia peaks early following infection, plateaus for 1–2 days, and then declines [42]. Active viral replication can be appreciated in the lymph nodes and splenic endothelial cells during viremia [43]. Virus replication also occurs in the bone marrow, providing a potential explanation for the severe bone pain experienced by many patients infected with dengue [44].

Severe dengue disease is thought to be a result of a complex cascade of immunopathologic events generating a "cytokine storm" [45] that leads to increased capillary permeability, endothelial leak, and plasma extravasation. When severe dengue occurs, it typically becomes clinically apparent between days 3 and 6 of the illness, progressing rapidly to hypovolemic or hemorrhagic shock [46]. The life-threatening illness can be further worsened if there is also a component of cardiogenic shock [47]. Severe dengue can be seen

secondary to infection with any of the four serotypes but is perhaps more common when certain serotype infections occur in a specific sequence [48, 49].

Several risk factors for severe dengue have been identified. Epidemiologic data suggests that there is an increased incidence of severe dengue during an individual's second infection [50]. It is theorized that this greater frequency may be related to preexisting antibodies generated in response to a previous infection with a different dengue. The preexisting antibodies could enhance the subsequent dengue infection by facilitating more efficient uptake of virus via immune complex-Fc receptor cell interactions [51, 52].

## 35.8 Clinical Features of Yellow Fever

The clinical presentation of YF ranges from a mild self-limited febrile illness to viral hemorrhagic fever and death. The incubation period for YF is 3–6 days following the bite of an infected female mosquito. Yellow fever is described classically as a biphasic disease. During the first phase of illness, the patient develops fever, myalgia, conjunctival injection, headache, and vomiting [53]. Yellow fever is one of a small number of infections associated with *Faget's sign*, a relative bradycardia with respect to temperature elevation [34] [▶ Call Out Box 35.2]. The majority of illness ends after this phase, but approximately 20% will go on to a "period of intoxication" following a 24- to 48-h period of remission [54]. The "period of intoxication" is characterized by high fever, profound weakness, abdominal pain, bleeding diathesis, and somnolence. This stage also features a characteristic hematemesis that the inhabitants of the New World named "vomito negro (black vomit)." It is in this stage where hyperbilirubinemia, hepatitis, and coagulopathy are seen. The impressive magnitude of hepatitis helps to distinguish YF from other viral hemorrhagic fevers. The hyperbilirubinemia is associated with moderate to severe jaundice, explaining how "yellow fever" got its name. Clinically significant myocardial damage and central nervous system dysfunction can occur. Between 20% and 50% of patients reaching the period of intoxication will not survive the infection [55].

The diagnosis of YF can be made on clinical grounds based on the patient's history and physical examination findings; viral detection during early viremia is important for public health reasons. The risk of person to person spread either from direct exposure to infected blood or from infected mosquitos having fed on the viremic patient. Infection control precautions should include having ill patients enclosed under a bednet to reduce the chances of this possibility. In the proper epidemiologic and clinical setting, identification of IgM to the yellow fever virus using ELISA supports the diagnosis [56, 57]. ELISA is limited by high cross-reactivity observed across flaviviruses, including dengue and Zika viruses [58, 59]. Real-time reverse transcriptase polymerase chain reaction (RT-PCR) is also available and is the test of choice during the period of infection when the patient is viremic [60]. Rapid molecular assays for testing with low detection limits and rapid processing time have also been developed [61]. Immunocytochemistry can also be used to detect yellow fever virus in organ parenchyma at autopsy [62].

**Call Out Box 35.2**
Liebermeister's rule states that every 1 °C increase in body temperature is associated with eight additional heartbeats per minute. A small number of infectious diseases break this rule. The few exceptions are associated instead with Faget's sign, bradycardia in the presence of fever. Dr. Jean Charles Faget studied yellow fever in Louisiana during the mid-1800s and noted this paradoxical association. A small number of other infections were subsequently noted to show the same unusual finding including typhoid fever, tularemia, brucellosis, Colorado tick fever, and, less commonly, pneumonia caused by *Legionella pneumophila*.

## 35.9 Clinical Features of Dengue

Like yellow fever, dengue infection has a broad range of clinical presentation. The World Health Organization had previously defined three distinct categories to dengue infection: (1) dengue fever, (2) dengue hemorrhagic fever, and (3) dengue shock syndrome. This classification has since been revised to (1) dengue without warning signs, (2) dengue with warning signs, and (3) severe dengue [63]. The prototypical dengue infection without warning signs begins 4–7 days after being bitten by the infected female mosquito vector. The patient develops an acute febrile illness with retro-orbital headache, generalized myalgias, arthralgias, and rash. The confluent maculopapular rash is more commonly seen in children than in adults [64]. Most dengue infections are either mild or asymptomatic [65]. The classification of "dengue with warning signs" captures cases which may be experiencing plasma leakage or bleeding and includes symptoms such as persistent abdominal pain and vomiting, minor mucosal bleeding, and/or lethargy. Acute gingival bleeding, heavy menses, erythematous and hemorrhagic skin and mucosal plaques, and even osteonecrosis of the jaw may occur [66]. Any variation of dengue can include hepatic manifestations from asymptomatic elevation of transaminases and mildly elevated bilirubin to acute liver failure [67]. Reported neurologic sequelae of dengue include encephalitis, Guillain-Barré syndrome, and ophthalmitis [68]. Vertical transmission has been reported secondary to dengue infection in pregnancy [69]. Unlike Zika virus infection, dengue infection during pregnancy does not appear to be associated with low birthweights or specific congenital malformations such as severe microcephaly [70, 71].

The classification of severe dengue includes many of the clinical manifestations described in prior definitions of dengue hemorrhagic fever and dengue shock syndrome. Severe dengue manifests as plasma leakage with the potential for shock, severe bleeding, multi-organ failure, and death. Thrombocytopenia leading to spontaneous ecchymosis and mucosal bleeding is not uncommon. A variety of pulmonary complications have also been described including pneumonitis, pulmonary edema, pulmonary hemorrhage, acute

**Call Out Box 35.3**
Yellow fever, dengue, Zika, and chikungunya viruses are all transmitted by female *Aedes aegypti* mosquitos. Unlike the vectors for malaria (various *Anopheles* species) and West Nile virus (*Culex* species), which bite primarily in the evening and at night, *Aedes aegypti* mosquitos are typically day-biters.

respiratory distress syndrome, hemoptysis, and pleural effusions [72]. Hemophagocytic lymphohistiocytosis has also been described in patients with severe dengue [73]. It is difficult to determine the case fatality rate from severe dengue due to the heterogeneity of presentations and the limited health-care resources in many developing nations where dengue is endemic. Patients who are treated in experienced centers have mortality rates less than 1% [74].

The signs and symptoms of dengue infection overlap with other acute febrile illnesses such as chikungunya, yellow fever, hantavirus, and influenza making a clinical diagnosis challenging. Complaints of fever and joint pain are not uncommon from any of them, but patients who develop chronic arthritis post-infection are most typically seen after chikungunya virus infection. The spread of Zika virus infection in areas where dengue is already endemic has made clinical diagnosis even more difficult [▶ Call Out Box 35.3]. Most dengue cases are still diagnosed clinically in the setting of an outbreak or limited resources. The diagnosis can be confirmed using a rapid serum NS1 antigen detection assay or through the detection of dengue-specific immunoglobulin M. Advanced and reference diagnostic laboratories may have access to dengue-specific polymerase chain reaction-based assays. Viral isolation in tissue culture and the measurement of serum neutralizing antibodies are typically reserved for reference laboratories or the research setting [75, 76].



## 35.10 Treatment and Prevention of Yellow Fever

There are no approved antiviral medications available to treat yellow fever. In hamster models, interferon therapy has shown mixed results [77]. Ribavirin has been shown to inhibit YF virus in cell culture, but its effects have not been demonstrated in higher-order animal models [78]. The backbone of treatment is largely supportive care in a hospital setting equipped to provide close clinical monitoring and care especially during the manifestations of severe yellow fever [79]. Practices of avoiding medications with active hepatic metabolism, reversing coagulopathy with blood products and using vasopressors and inotropes, as appropriate, to support the cardiovascular status, are key components. Medications with potential to inhibit platelet function should also be avoided.

Yellow fever is a vaccine preventable infection. The 17D live attenuated yellow fever vaccine has been available worldwide since shortly after its discovery in 1937 by Max Theiler [80]. The vaccine is given as a 0.5 mL subcutaneous injection and is currently recommended for anyone traveling to yellow fever-endemic areas of Africa or South America. A booster dose was once recommended every 10 years; however a single lifetime dose is now considered adequate except in circumstances with known and recurrent high-risk exposures [81]. During the global vaccine shortages associated with the Angola YF outbreak of 2016, fractional dosing using one fifth of standard vaccine dose was attempted and found to be successful [82]. Rare but potentially severe side effects of the vaccine include yellow fever vaccine-associated viscerotropic disease, a vaccine-associated complication that mimics wild-type yellow fever. Vaccine-associated viscerotropic disease should be suspected in anyone presenting with hepatitis and high fevers following vaccine administration. The true incidence of this complication is uncertain [83]. Yellow fever vaccine-related neurotrophic disease has also been described. This complication presents with signs and symptoms of meningoencephalitis, myelitis, or Guillain-Barré syndrome following vaccine administration. Rates of vaccine-associated viscerotropic disease and vaccine-related neurotrophic disease have been reported as 0.3 and 0.8 per 100,000 doses, respectively [84]. Individuals 60 years of age and older have higher rates of adverse vaccine-associated outcomes [85]. Despite the rare, serious complications that can be associated with yellow fever vaccine, it remains one of the safest and most effective immunizations ever developed. Plans are underway to administer more than 174 million doses to individuals living in the endemic areas of Africa and Latin America between 2011 and 2020 [83].

## 35.11 Treatment and Prevention of Dengue

An evidence-based management algorithm for treating dengue, including criteria for hospital admission and discharge, has been developed under the leadership of the World Health Organization. Like the treatment of YF, supportive care is the mainstay in caring for those with dengue. Any of the following symptoms should prompt close clinical observation in a hospital setting: abdominal pain, clinical fluid accumulation (ascites or pleural effusions), bleeding mucosa, lethargy, or hepatomegaly [86]. Sustained abdominal pain, intractable vomiting, change from fever to hypothermia, severe lethargy on presentation, and hematocrit/hemoglobin ratio $\geqslant$3.5 have all been seen as clinical alarm symptoms placing patients at increased risk for deterioration during hospitalization [87]. The period around defervescence is the time of greatest clinical risk for transition to severe dengue. As with YF, fever and discomfort should be treated with acetaminophen-based antipyretics rather than aspirin or NSAIDS to reduce bleeding risk. Plasma leakage requires prompt and judicious (i.e., highly controlled) treatment with intravascular volume repletion and, when required, blood products and vasopressors [88]. Treating dengue requires assessment, intervention, and reassessment to avoid delivering too much fluid causing pulmonary edema. Like YF, there are no approved specific antiviral medications licensed for the prevention or treatment of dengue. Chloroquine, corticosteroids, lovastatin, and balapiravir have all been explored

in clinical treatment trials but failed to meet endpoints for significantly reducing viremia or NS1 antigenemia or improving clinical outcome [89–92].

Development of a dengue vaccine remains a high priority worldwide as it has for the last 75 years. A live attenuated tetravalent vaccine designed to prevent dengue using a molecular clone of the yellow fever virus 17D strain as a backbone was developed, studied, and approved in 20 endemic countries. Its moderate overall efficacy against dengue of all severities, variance in efficacy against specific dengue serotypes, and safety concerns among young recipients without preexisting immunity to at least one dengue virus serotype at the time of vaccination have resulted in limited vaccine uptake [93]. Until a highly efficacious vaccine is readily available, mosquito control remains the most commonly used tool to reduce the dengue burden [94]. Use of insecticides and newer, novel methods such as deploying *Wolbachia*-infected mosquitoes are options for vector control, but their effectiveness at preventing human infections and disease has yet to be demonstrated [95].

## 35.12 Exercises

Please refer to the supplementary information section for answers to these exercises.

? Each of the numbered descriptions listed in the left panel is best associated with *one* of the five viruses listed in the right panel. Match each numbered item to the virus most fitting of the description.

| Pathogen | Characteristic finding |
|---|---|
| 1. Infection is asymptomatic most of the time, but acute infection does cause fever, rash, and conjunctivitis in some individuals | A. Dengue |
| 2. Joint pain is a typical complaint during acute infection. Post-infection chronic arthritis can be particularly problematic | B. Yellow fever |
| 3. There are four major serotypes | C. Zika |
| 4. A highly effective vaccine is currently available to prevent infection | D. West Nile |
| 5. This virus is not transmitted by *Aedes aegypti* mosquitos | E. Chikungunya |
| 6. The clinical observation of paradoxical bradycardia is most typical during infection with this virus | |
| 7. Infection causes severe bone pain explaining the nickname "breakbone fever" | |
| 8. A 20–50% mortality rate is expected when infection progresses to a "period of intoxication," heralded by the development of hyperbilirubinemia, hepatitis, coagulopathy, and "black vomit" hematemesis | |
| 9. Infections are transmitted by mosquitos that bite during the evening and at night | |
| 10. During infection, defervescence marks the period of greatest risk for progression to severe disease | |

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# Chagas Disease: South American Trypanosomiasis

## Fever, Myalgias, and Acute Myocarditis in a Traveler Returning From a Trip to the Amazon Rain Forest

*Joseph F. Toth III and Joseph Domachowske*




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**Learning Objectives**

- Describe the clinical presentations of acute and chronic forms of Chagas disease
- Explain how the symptomatology of Chagas disease dictates the preferred treatment options
- Appreciate the usual patterns of illness as Chagas disease progresses over time

**Call Out Box 36.1**

Dr. Carlos Chagas discovered American trypanosomiasis in 1909. The trypanosome parasites that cause African sleeping sickness are a different species, are transmitted by a different arthropod vector, and cause a very different disease. American trypanosomiasis only occurs in the Americas, and African trypanosomiasis only occurs in Africa.

## 36.1 Definitions

**Chagoma** - An inflammatory nodule that develops at the bite site of the triatomine insect that arises secondary to a type IV hypersensitivity reaction.

**Romaña's sign** - The clinical triad of periorbital soft tissue and eyelid swelling, conjunctivitis, and ipsilateral preauricular lymphadenopathy seen when the trypanosome inoculation site is at or near the conjunctivae.

**Dilated cardiomyopathy** - Enlargement of the heart associated with myocardial dysfunction and common cause of heart failure.

**Achalasia** - A disorder of esophageal motility caused by dysfunction, degeneration, or absence of ganglion cells in the myenteric plexus. The lower esophageal sphincter fails to relax leading to sensations of dysphagia and early satiety.

**Trypomastigote** - A stage in in the trypanosome life cycle where the flagella is posterior to the nucleus with an undulating membrane running along the length of the organism.



## 36.2 Introduction

Chagas disease is one of the most common parasitic infections in the world. Although it is endemic in the countries of Central and South America, it is also becoming of increasing concern within the United States as individuals from endemic regions relocate. Currently, there are an estimated 300,000 infected individuals living in the United States [1] [▶ Call Out Box 36.1].

Chagas disease is caused by the protozoan parasite, *Trypanosoma cruzi,* which is transmitted to humans when they are bitten by an infected triatomine insect. This arthropod vector can be found spanning from as far south as Argentina and as far north as Maryland. The transmission of Chagas disease is highest in rural areas with poor housing infrastructure and sanitization measures. Triatomine insects often inhabit the homes of the people it infects [1, 2].

Human infection is categorized into an acute phase, an indeterminate phase, and a chronic phase based on the patient's clinical signs and symptoms [2].

The acute phase of Chagas disease lasts for 8–12 weeks. Patients will often be asymptomatic. When signs and symptoms do occur, they are typically nonspecific. Fever, lymphadenopathy, hepatosplenomegaly, and myalgias are all fairly characteristic. Less commonly patients present with acute myocarditis [2]. Less common but highly specific clinical features include the presence of a **chagoma** at the site of inoculation, or a positive **Romaña's sign**, both of which are virtually pathognomonic for Chagas disease [3]. A chagoma is an inflammatory subcutaneous nodule present at the site where the patient was bitten. Romaña's sign is the clinical triad of periorbital soft tissue and eyelid swelling, conjunctivitis, and ipsilateral preauricular lymphadenopathy. These findings occur when the *T. cruzi* protozoan enters through the conjunctivae, or when the bite site is near the eye.

Unfortunately, only about 10% of Chagas disease cases are accurately diagnosed and treated during the acute phase of infection largely due to the nonspecific clinical manifestations. During the acute phase of infection, parasitemia is readily detected on a routine peripheral blood smear. (◘ Fig. 36.1).

Following the acute phase of infection, the disease progresses to an indeterminate phase that is defined by a lack of any clinical, radiographic, or electrocardiographic abnormalities [2]. It's during the intermediate phase that 70–90% of patients recover from the infection. Following the indeterminate phase, between 10 and 30% of patients will progress to the determinate phase that defines chronic Chagas disease [2]. Chronic infection leads to cardiac involvement, gastrointestinal involvement, or both. Cardiac pathology is more common. Symptoms of myocardial involvement may include those seen with congestive heart failure such as dyspnea or peripheral edema. Common gastrointestinal symptoms are associated with achalasia or megacolon such as dysphagia or constipation. Malnutrition secondary to poor intestinal absorption is also common. A biopsy of tissue suspected to be chronically infected, such as the myocardium or the colon, may be required to confirm the diagnosis [4]. The determinant phase of Chagas disease is associated with a poor prognosis; more than half of such patients will die from heart failure [5]. (◘ Fig. 36.2).

## 36.3 The Life Cycle of *T. cruzi* (◘ Fig. 36.3)

When the triatomine insect takes a blood meal from an infected host, it ingests the *T. cruzi* trypomastigotes. Within the midgut of the vector, the parasite transforms into an

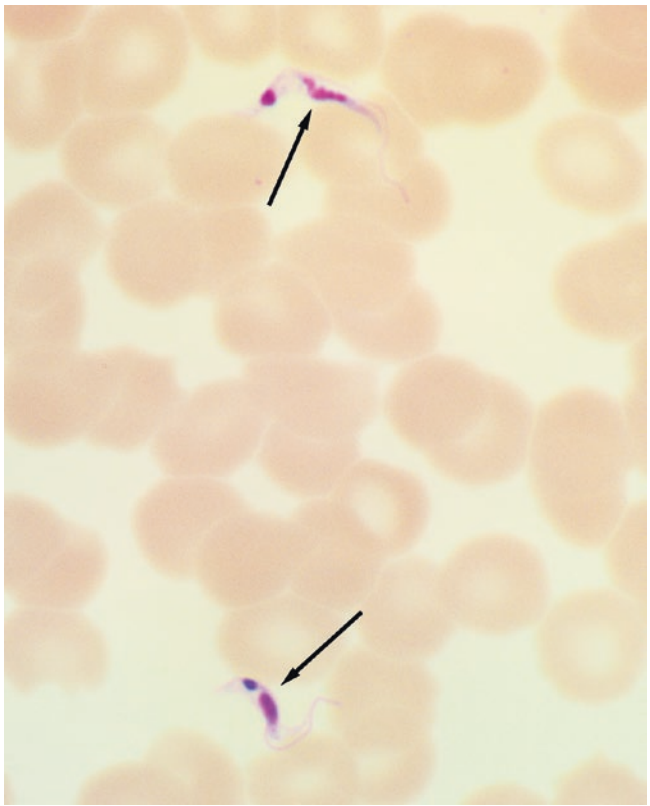

**Fig. 36.1** Shown is the peripheral blood smear of a patient with acute Chagas disease. Two *Trypanosoma protozoa* are seen (*arrows*). (Image kindly provided by Dr. Scott Riddell)

epimastigote and undergoes replication via binary fission. In the hindgut of the insect, the parasite undergoes further transformation into metacyclic trypomastigotes with full motility capabilities using a flagellum as its primary virulence factor [7]. When the triatomine insect takes a second blood meal, the insect defecates at the site of the bite [3]. Its fecal matter contains the *T. cruzi* trypomastigotes. The trypomastigotes infect several different cell types at the site of the bite transforming into amastigotes. Amastigotes transform into trypomastigotes, emerge from the infected cell, and enter the bloodstream. From the bloodstream, other tissue types including cardiac muscle and smooth muscle along the gastrointestinal tract [3] become infected. During parasitemia, additional bites from triatomine insects allow the cycle to continue.

## 36.4 Clinical Features of Chagas Disease

The manifestations of Chagas disease during the acute phase of infection may include systemic signs and symptoms such as fever, chills, and myalgias. Patients with myocarditis can experience fatigue, dizziness, syncope, dyspnea, peripheral edema, palpitations, or electrocardiographic abnormalities. Gastrointestinal manifestations of Chagas disease can include constipation, dysphagia, early satiety, and intestinal malabsorption [8]. Progression of esophageal dysfunction is monitored by a barium swallow and upper endoscopy.

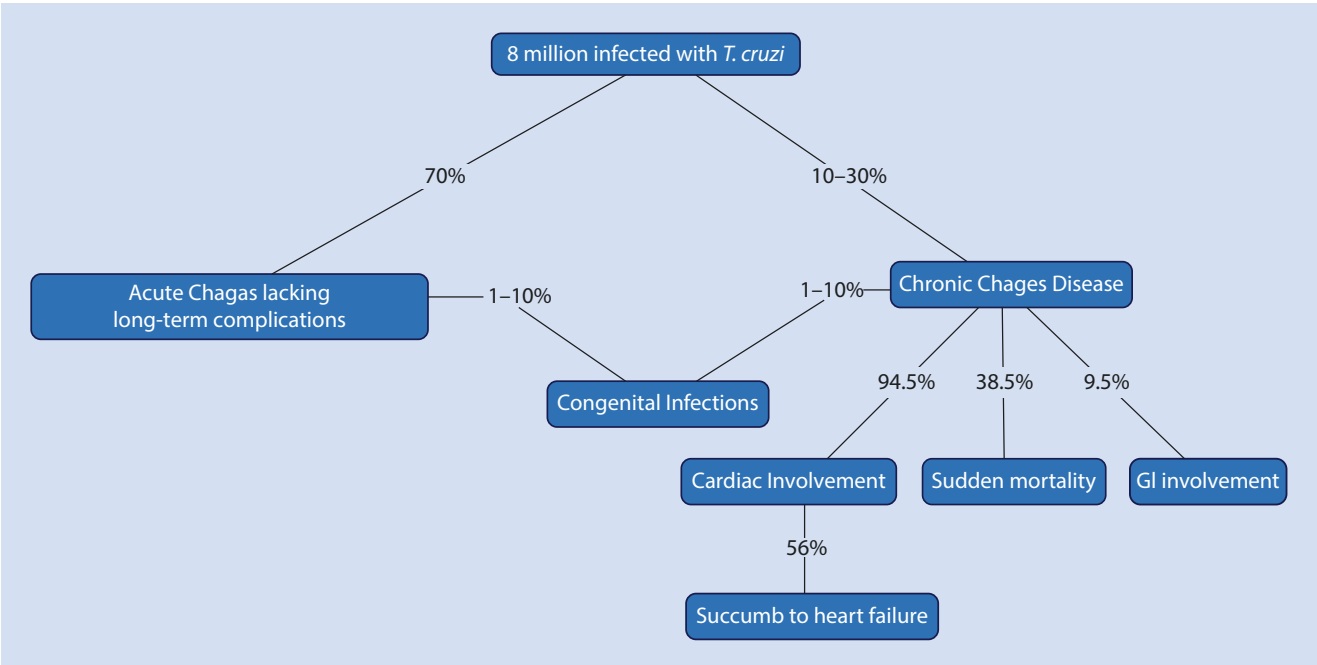


**Fig. 36.2** Shown are the relative frequencies of the common manifestations of Chagas disease and their sequelae

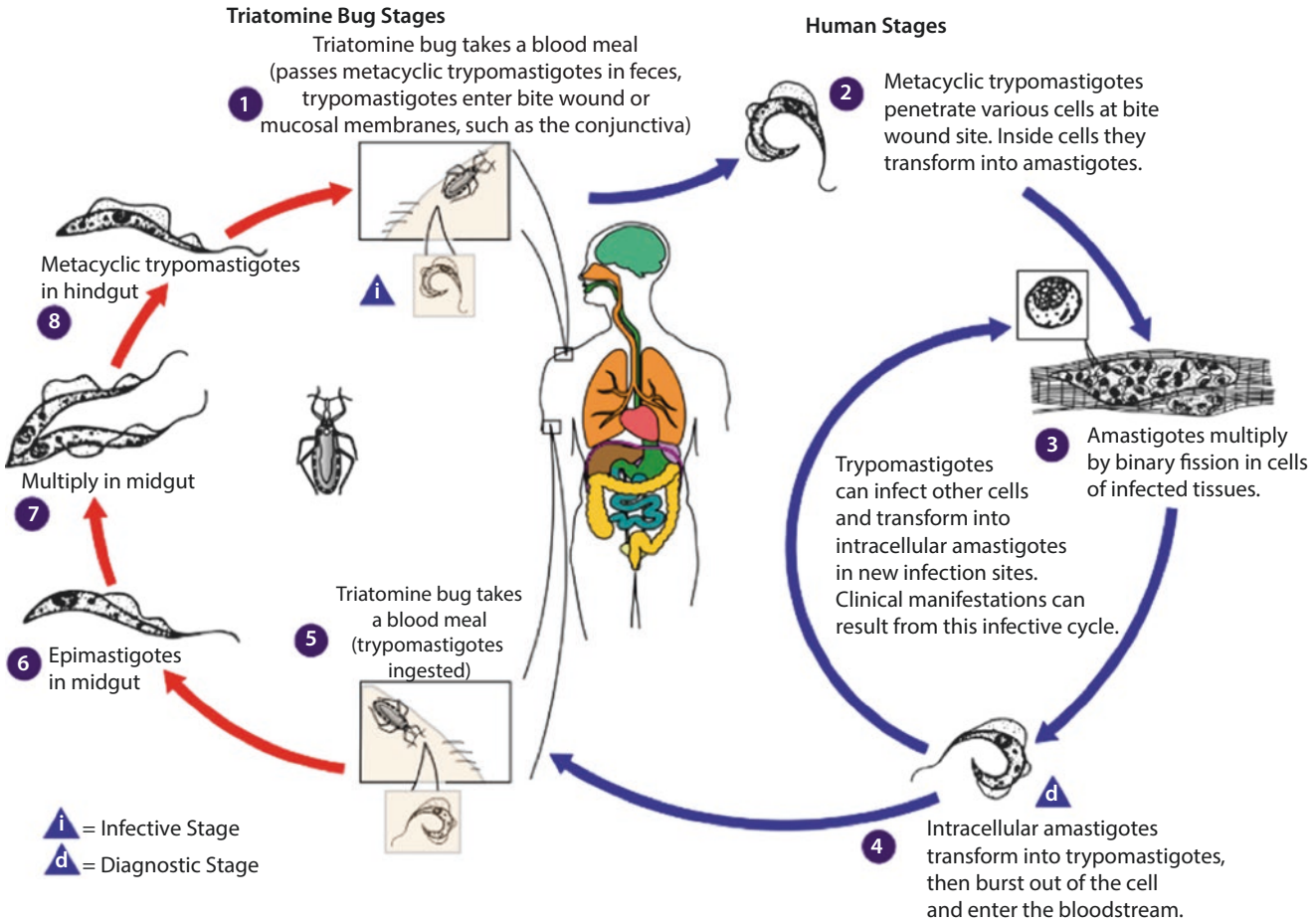


**Fig. 36.3** Shown is the life cycle of *T. cruzi*. (Image reprinted from: [6])

A minority of patients will still have a chagoma at the site of the insect bite, and an even smaller number will present with Romaña's sign [2].

The diagnosis of acute Chagas disease can be confirmed by performing a peripheral blood smear. Extracellular *T. cruzi* trypomastigotes are easily spotted (Fig. 36.1). A Giemsa stain may demonstrate the intracellular presence of *T. cruzi* amastigotes (Fig. 36.4). Patients who are diagnosed with acute Chagas disease should be treated with antiparasitic medication as soon as feasible to avoid further disease progression.

HIV-infected patients with CD4+ T cell counts below 200 cells per microliter have the potential to reactivate previously controlled disease. Chagas disease reactivation can also occur in patients undergoing chemotherapy for a malignancy and individuals being treated with immunosuppressive medication regimens after solid organ or bone marrow transplant. Clinical findings of infection in immunosuppressed patients include erythema nodosum, progressive myocarditis, meningoencephalitis, or, quite rarely, parenchymal brain infection [10]. The cerebral abscesses seen during Chagas reactivation may be confused with central nervous system toxoplasmosis.

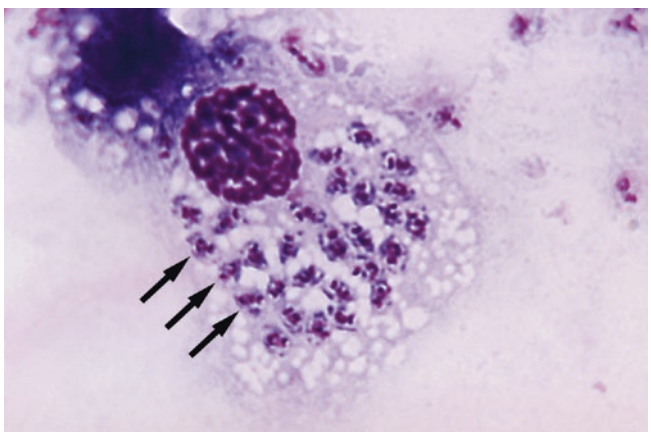

**Fig. 36.4** Shown is a Giemsa stain of a peripheral blood mononuclear cell with more than two dozen *T. cruzi* intracellular amastigotes [9]

## 36.5 The Treatment of Chagas Disease

Treatment is recommended for all cases of congenital, reactivated, acute, and chronic Chagas disease in children. Treatment is strongly recommended for adults up to 50 years old with chronic infection unless they have already developed

dilated cardiomyopathy. For adults older than 50 years, treatment decisions should be individualized based on perceived benefits and potential risks.

Two medications, benznidazole and nifurtimox, have shown similar effectiveness when used to treat infection secondary to *T. cruzi*. Benznidazole is approved by the US Food and Drug Administration (FDA) for use in children and adults but is not yet available in US-based pharmacies. Nifurtimox is not currently FDA approved for this indication [11]. Both drugs are currently available by request from the US Centers for Disease Control and Prevention. Side effects are fairly common with these medications especially in older adults, although benznidazole is generally better tolerated making it preferable to nifurtimox under most circumstances [11]. Questions related to the treatment of Chagas disease, or regarding the logistics of obtaining either medication, can be directed to the US Centers for Disease Control and Prevention's Parasitic Diseases Public Inquiries (404–718-4745; e-mail ► chagas@cdc.gov).

Benznidazole renders *T. cruzi* trypomastigotes and amastigotes unable to reduce toxic reactive oxygen species, thereby acting as a potent trypanocidal drug [11]. Benznidazole is excreted primarily by the kidneys. The drug may have adverse effects on the bone marrow and liver, so baseline laboratory studies, including a complete blood count, serum hepatic transaminases, bilirubin, creatinine, and blood urea nitrogen, should be performed prior to starting treatment [12]. Common side effects of benznidazole include dermatitis, peripheral neuropathy, anorexia, and weight loss [3]. Contraindications to and precautions for the use of benznidazole include pregnancy, age greater than 50 years, and severe renal or hepatic insufficiency.

## 36.6 Cardiac and Intestinal Treatment Interventions for Chagas Disease

Patients with chronic Chagas disease regularly develop congestive heart failure. Providers should generally follow current general guidelines for managing congestive heart failure, keeping in mind that the cardiac pathology in Chagas disease frequently triggers bradyarrhythmias. Typical interventions used in the management of congestive heart failure, such as angiotension-converting enzyme (ACE) inhibitors or beta-adrenergic antagonist (beta-blockers), may not be well tolerated. Amiodarone is a suitable option for patients with ventricular tachycardias [12]. As disease advances, the placement of a pacemaker may be necessary. Cardiac transplantation is the only possible cure for advanced cardiac disease.

Patients with gastrointestinal manifestations of chronic Chagas such as megaesophagus and megacolon may require surgical management to relieve related symptoms such as dysphagia and constipation.

**Case Study**

### Clinical Cases

**Case 1**

A 6-year-old boy presents with fevers and fatigue the past 2 days. The patient's mother also expresses concern about her son's swollen right eye. The present illness is also associated with several episodes of diarrhea. A detailed social history reveals that the patient and his mother just returned from a month-long trip to Brazil. On physical examination, the boy is febrile. Lymphadenopathy is appreciated along the right anterior and posterior cervical lymph node chains and in the right preauricular area. There is erythema and periorbital swelling noted around the boy's right eye. The bulbar and palpebral conjunctivae are injected (■ Fig. 36.5). Laboratory test results showed a normal complete blood count. Thick and thin "malaria smears" were negative for the presence of intraerythrocytic or extracellular forms of *Plasmodium* species which demonstrated the presence of trypomastigotes (■ Fig. 36.1). The diagnosis of acute Chagas disease was made, and the patient was started on benznidazole therapy after conferring with experts at the US Centers for Disease Control and Prevention.

**Case 2**

A 47-year-old male presents to medical care with bilateral peripheral lower extremity edema. He states that he needs a "water pill" as told by one of his friends. The history of present illness reveals that the patient has experienced a 10-pound weight gain. The patient is an immigrant from South America who has lived in the United States for the past 25 years. A chest radiograph shows evidence of cardiomegaly, and an electrocardiogram shows a right bundle branch block pattern with bradycardia. An echocardiogram reveals biventricular dilation and impaired myocardial function consistent with dilated cardiomyopathy. A biopsy of the heart is performed showing *T. cruzi* amastigotes in the cardiac muscle (■ Fig. 36.6). Given the patient's age and progression of disease, a diagnosis of chronic Chagas disease is made, and the patient is started on benznidazole therapy in an effort to delay disease progression.

## 36.7 An Example of Chagas Disease Prevention: A Public Health Effort in Ecuador

Public health strategies to curb the transmission of Chagas disease in endemic regions of the Americas have been highly successful. For example, public health efforts in Ecuador have included surveillance for and abatement of the triatomine insect vector through targeted insecticide application in parallel with educational programs designed to improve community awareness and knowledge about *T. cruzi* infection. Residents are engaged and interviewed in their homes, schools, and places of work. Local public health personnel search homes, brush, and

**Fig. 36.5** Child demonstrating Romaña's sign of the right eye [13]

**Fig. 36.7** Shown is an image of the triatomine insect vector for Chagas disease. The insects are also referred to as kissing bugs, reduviid bugs, assassin bugs, vampire bugs, conenose bugs, barbeiros, vinchucas, pitos, and chinches. (Image kindly provided by Froilan Heras)



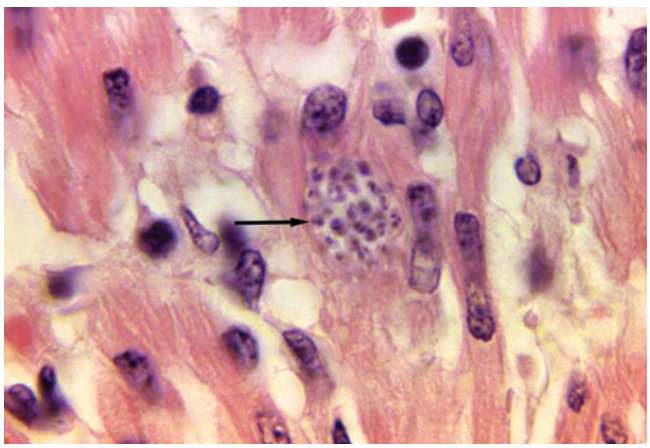

**Fig. 36.6** Shown is a section of a myocardium biopsy stained with hematoxylin and eosin. A myocardial fiber containing a pseudocyst of *T. cruzi* amastigotes is identified by the arrow [14]

fields in regions known to have a high prevalence of Chagas disease to collect triatomine insects (Fig. 36.7). Once captured, the insects are tested for *T. cruzi* infection. If the results are positive, nearby residents are systematically tested for infection. This collaboration between the local public health teams and the national government of Ecuador has been very effective in reducing the triatomine vector population and in providing treatment to infected individuals before they become symptomatic.

## 36.8 Exercises

Please refer to the supplementary information section for answers to these exercises.

1. A 28-year-old male presents with fever, myalgias, and acute chest pain. He has no chronic health problems. His family history is negative for heart disease. On physical examination, he has an erythematous nodule present on his left forearm. The patient states that he first noted the nodule 3 weeks ago while he was in Ecuador on a medical mission trip. A chest radiograph and electrocardiogram are normal. Of the following options, the most appropriate next step in this patient's medical care is to:
   (a) Request an abdominal computer tomography scan
   (b) Request a thick and thin blood smear
   (c) Prescribe nifurtimox
   (d) Prescribe benznidazole
   (e) Request testing for antibodies against *Trypanosoma cruzi*

2. Which ONE of the following is a true statement?
   (a) A vaccine for Chagas disease is available
   (b) *Trypanosoma cruzi* is a multicellular parasite transmitted by an insect
   (c) *Trypanosoma cruzi* infection is transmitted to human's host through the vector's feces
   (d) Chronic Chagas disease is associated with minimal morbidity
   (e) Acute Chagas disease is endemic to most of tropical South America, Africa, and Asia

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### Further Reading

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# Leptospirosis

## A Farmer with Fever, Conjunctival Suffusion, and Rash Who Subsequently Develops Jaundice and Hepatomegaly

*Daniel Lichtenstein and Joseph Domachowske*




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**Learning Objectives**

- Describe the pathogenesis of leptospirosis
- List the known risk factors for *Leptospira* infection
- Recognize the biphasic clinical presentation of leptospirosis, and identify characteristics of the illness that can be used to distinguish it from other illnesses that present with similar symptoms
- Describe the known complications of leptospirosis
- Develop a management plan for a patient with suspected or confirmed *Leptospira* infection

## 37.1 Background

Among the many different *Leptospira* species identified, eight cause disease in humans. The division of each species into serologic variants is more important for epidemiologic tracking than it is for diagnosis or management. Leptospirosis is a leading cause of zoonosis worldwide. The bacteria normally reside in the renal tubules of animals including livestock and rodents and are shed in their urine, explaining why a key risk factor for the development of leptospirosis is direct or indirect exposure to animal urine. The bacteria can survive in warm, wet environments for several weeks if the soil remains damp and the water has a neutral to slightly alkaline pH. *Leptospira* can thrive in warm freshwater lakes and ponds, but do not survive in brackish or seawater.

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## 37.2 Transmission of *Leptospira* Species to Humans

Most cases of leptospirosis occur after an individual is exposed to water that has been contaminated by a *Leptospira* species. Animal urine containing the bacteria can gain entry to lakes, ponds, and puddles. Individuals who are then exposed to the contaminated water may become infected when the bacteria invade across mucous membranes or through breaks in the skin. Less commonly, transmission occurs via direct contact with infected animals. Other very uncommon modes of infection include vertical, sexual, and breast milk transmission. *Leptospira* species infection is rare during pregnancy, but when it does occur, fetal loss exceeds 50% [► Call Out Box 37.1].

**Call Out Box 37.1**
Leptospirosis is an uncommon zoonotic infection transmitted to humans via direct or indirect exposure to animal urine contaminated by one of several *Leptospira* species of bacteria

## 37.3 The Biphasic Disease Course of Leptospirosis

Leptospirosis is a biphasic infection: During the **leptospiremic phase**, *Leptospira* are present in the bloodstream, essentially showering the patients' organs and tissues with bacteria. Following this period of hematogenous seeding, fever and other systemic signs of illness abate, and the patient feels and appears well. Several days later, the **immune phase** of infection begins, and the patient again becomes symptomatic. The robust immune response directed against the bacteria is meant to eradicate the infection, but can also trigger pathologic immune-mediated complications in the host.

## 37.4 Phase I: Leptospiremia

Bacteria enter the host during an exposure to contaminated animal urine, water, or wet soil via the mucous membranes or break in the skin. Several days to 2 weeks later, systemic symptoms, including fever, herald the onset of bacteremia. During this **leptospiremic phase** of infection, the spirochete replicates in the bloodstream while evading innate host immunity. The blood delivers the bacteria to distant organs and tissues including the liver, kidneys, and eyes. The precise mechanism of innate host immune evasion is unclear, but probably involves the ability of pathogenic *Leptospira* to avoid activation of host toll-like receptor 4. Symptomatic patients develop an **acute, nonspecific febrile illness** of several days duration. When the fever and other associated symptoms abate, the patient looks and feels well.

## 37.5 Phase II: The Immune Phase of Leptospirosis

The asymptomatic window that follows phase I of infection lasts for several days before the patient begins to experience symptoms from the **immune phase** of leptospirosis. During this phase, complications arise secondary to direct *Leptospira* invasion as well as from the host-mediated adap tive immune response to the infection. Symptoms vary from individual to individual primarily based on the specific organs and tissues involved, but all patients have some degree of vascular endothelial damage that contributes to their complications. While the bloodstream and most organs and tissues are cleared of *Leptospira* rapidly, the organism can persist in the kidneys and in immune-privileged anatomic sites, such as the central nervous system and the eye, for longer periods of time. The **severe complications** of leptospirosis, including **Weil disease**, occur during the immune phase of infection.

## 37.6 Epidemiology of Leptospirosis

Leptospirosis is underdiagnosed and underreported. The major risk factor for infection is exposure to animal urine or water sources that have been contaminated by it. Age and gender are known secondary risk factors, with the highest rate of infection seen among young adult men. Men aged 20–49 account for 48% of all cases and 42% of all deaths from leptospirosis.

Cases of leptospirosis can occur anywhere, but reports of disease are heavily concentrated to tropical and sub-tropical areas of the world, where its prevalence is highest in resource-poor countries during rainy seasons. The World Health Organization (WHO) estimates that *Leptospira* affects 10 of every 100,000 people living in the tropics annually. Rural farming areas are associated with the highest disease burden, though urban slums are predicted to account for an increasingly large percentage of cases due to climate change and population growth. Occupations related to farming, agriculture, fishing, and veterinary medicine increase the risk for infection. Rodents also transmit the disease, explaining why sewage workers have an increased incidence of leptospirosis (◘ Fig. 37.1). A complete list of high-risk groups can be found in the WHO 2003 leptospirosis guidelines available at ► http://www.who.int/topics/leptospirosis/en/.

**Call Out Box 37.2**
Consider a common-source outbreak of leptospirosis when several individuals from the same community present with similar symptoms 1–2 weeks after potential exposure such as a flood.

**Heavy rainfall** and **flooding** are associated with leptospirosis outbreaks. The WHO estimates that *Leptospira* affect up to 100 of every 100,000 people in tropical regions during an epidemic, a tenfold increase above normal rates. Those participating in **recreational watersports** also have an increased risk for infection, especially for patients presenting in regions where the disease is not endemic. Leptospirosis is one of the most common zoonoses in the world with an estimated one million new cases and 60,000 deaths caused by the disease each year [► Call Out Box 37.2].

## 37.7 Clinical Presentation and Diagnosis of Leptospirosis

Classic leptospirosis presents as a biphasic illness 5–14 days after exposure to animal urine or contaminated water. The leptospiremic phase lasts for up to 1 week and is followed by an asymptomatic period of up to 3 days duration. The

◘ **Fig. 37.1** Working barefoot in water, rice paddy farmers are among those at high risk for leptospirosis. (Pictures were obtained from the CDC Public Health Image Library, and taken by Evi Susanti Sinaga)

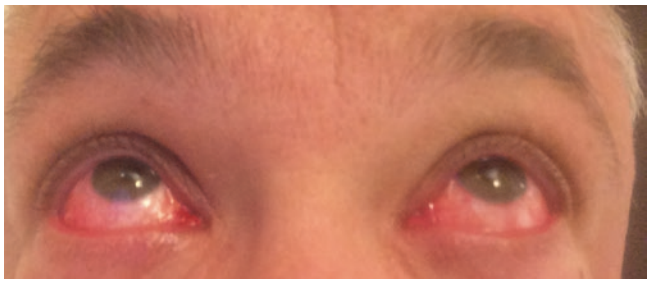

**Fig. 37.2** Shown is a patient with bilateral bulbar and palpebral conjunctival suffusions, a nonspecific but typical finding of leptospirosis during the bacteremic phase infection. (Image provided by Dr. Joseph Domachowske)

immune phase is marked by a variety of presentations, ranging from mild to severe, lasting for a variable period of time.

Leptospirosis presents similarly to other infections prevalent throughout the world, has nonspecific clinical and laboratory findings, and does not always follow a biphasic presentation. For these reasons, the **diagnosis cannot be made by history, physical examination, and screening laboratory results alone**. Definitive diagnostic tests are time intensive, relatively expensive, often require a high level of expertise to perform or interpret, and are not widely available, particularly across regions with the highest disease burden. Given the potential for severe complications if left untreated, **empiric antibiotic treatment should be administered anytime there is a strong clinical suspicion for leptospirosis.**

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### 37.7.1 Clinical Presentation: Leptospiremic Phase

The leptospiremic phase of infection is a nonspecific febrile illness. In addition to the abrupt onset of fever, symptoms may include myalgias, chills, headache, back pain, abdominal pain, diarrhea, vomiting, anorexia, cough, or sore throat. If the medical history includes potential exposure to animal urine or contaminated water, leptospirosis should be considered as a possible cause for the patient's fever.

On physical examination, findings may include hepatomegaly, conjunctival suffusion (Fig. 37.2), or rash.

Similarly presenting illnesses endemic to the region of exposure must be included in the differential diagnosis and ruled out, such as influenza, rickettsial disease, dengue fever, and malaria (Table 37.1).

### 37.7.2 Clinical Presentation: Immune Phase

Patients who are not recognized and treated for the infection during the leptospiremic phase will experience temporary relief from their symptoms for several days before the symptoms of the immune phase become apparent. The immune phase of leptospirosis is associated with one or more severe, organ-specific complications. Based on the organ systems most involved, illness is categorized into three groups:

1. **Central nervous system-dominated anicteric leptospirosis**
2. **Respiratory-dominated anicteric leptospirosis**
3. **Severe icteric leptospirosis, also known as "Weil disease"**

Complications do not always fit neatly into one category because substantial overlap can be seen across each of the groups.

Central nervous system-dominated anicteric leptospirosis is associated with fever, photosensitivity, headache, and stiff neck. Cough and fever are the prominent symptoms with respiratory-dominated anicteric leptospirosis. Hemoptysis may be seen. Pulmonary hemorrhage leading to respiratory failure is the leading cause of leptospirosis-associated mortality. Severe icteric leptospirosis, also known as Weil disease, is associated with fever. Patients with Weil disease develop varying degrees of pulmonary, renal, and hepatic complications, including jaundice, oliguria, and pulmonary hemorrhage (Fig. 37.3).

Weil disease is a severe manifestation of leptospirosis that results in significant morbidity and mortality.

Physical examination findings of central nervous system-dominated anicteric leptospirosis include fever, photophobia, and nuchal rigidity. Physical examination findings seen with respiratory-dominated anicteric leptospirosis include decreased breath sounds and basilar rales. In Weil disease, jaundice and hepatomegaly are observed. A petechial rash or other bleeding can be seen in all three presentations, and may involve the mucous membranes. Hypotension is common, and shock may occur.

Laboratory findings that may be seen during the immune phase of leptospirosis are summarized in Table 37.2.

## 37.8 Diagnostic Testing for Leptospirosis

The gold standard diagnostic test for leptospirosis is the determination of serum antibody titer using the microscopic agglutination test (MAT) to demonstrate a fourfold or greater rise in titers. Other available tests include bacterial culture, polymerase chain reaction, and antibody testing using an enzyme-linked immunosorbent assay (ELISA). *Leptospira* species are too small to be observed under standard light microscopy, but can be visualized using dark-field microscopy. When evaluating a patient for suspected leptospirosis, it is important to involve a clinical microbiologist to ensure that samples are collected properly and sent to appropriate referral laboratories. The Centers for Disease Control and Prevention (CDC) accepts samples thought to be infected with *Leptospira* species for diagnostic testing and for epidemiological purposes. Guidelines can be found on their "Infectious Disease Laboratory Test Directory" webpage: ▶ https://www.cdc.gov/laboratory/specimen-submission/list.html.

**Table 37.1** Differential diagnosis for a patient with suspected leptospirosis

| Clinical presentation | Possible alternative diagnoses | Overlapping findings with leptospirosis | Findings that favor leptospirosis | Additional notes |
|---|---|---|---|---|
| Acute, nonspecific febrile illness | Rocky Mountain spotted fever | Fever, rash, headache, myalgia, nausea, vomiting, abdominal pain thrombocytopenia, hepatic transaminitis | No potential tick exposure, conjunctival suffusion | Oral doxycycline is used to treat either infection |
| | Endemic typhus | Fever, chills, rash, headache, myalgia, cough, nausea, vomiting, thrombocytopenia, exposure to rodent excreta | Conjunctival suffusion | Oral doxycycline is used to treat either infection |
| | Ehrlichiosis | Fever, rash, headache, nausea, vomiting, abdominal pain thrombocytopenia, hepatic transaminitis | No potential tick exposure, conjunctival suffusion | Oral doxycycline is used to treat either infection |
| | Dengue fever | Fever, rash, headache, myalgia, vomiting, thrombocytopenia, hepatic transaminitis, transmission during rainy season | Conjunctival suffusion | Treatment for dengue infection is supportive |
| Central nervous system-dominated anicteric leptospirosis | Aseptic viral meningitis, Lyme meningitis | Fever, headache, photophobia, nuchal rigidity, rash, nausea, vomiting, elevated CSF opening pressure, normal CSF glucose, raised CSF protein, CSF lymphocytic pleocytosis | Conjunctival suffusion | Aseptic meningitis is discussed in ► Chap. 22 |
| Respiratory-dominated anicteric leptospirosis | Influenza | Fever, cough, headache, myalgia, pneumonia, respiratory failure. Biphasic presentation in severe disease | Illness occurring outside of the typical influenza season | Severe influenza is most common in the elderly, whereas leptospirosis is more common in young- and middle-aged adults |
| | Agents associated with atypical pneumonia, SARS, MERS | Fever, cough, headache, myalgia, pneumonia, respiratory failure | | Atypical pneumonia is discussed in ► Chap. 8 |
| Pulmonary leptospirosis with Weil disease (icteric leptospirosis) | Hantavirus | Fever, myalgia, headache, vascular leakage. Rodent exposure, recent travel to rural farming areas | Jaundice, conjunctival suffusion | Supportive treatment including fluid and electrolyte monitoring, cardiovascular support, and/or mechanical ventilation for respiratory failure may be necessary for either illness |
| Severe icteric leptospirosis; Weil disease | Infectious mononucleosis | Fever, headache, myalgia, hepatomegaly, rash, elevated hepatic transaminases and bilirubin, leukocytosis, thrombocytopenia | Conjunctival suffusion, biphasic presentation of illness | Atypical lymphocytosis, exudative pharyngitis, and splenomegaly are more suggestive of infectious mononucleosis |
| | Severe dengue infection, with hemorrhage | Fever, headache, myalgia, vomiting, rash, bleeding, abdominal pain, dyspnea, thrombocytopenia, transmission during rainy season, elevated hepatic transaminases and bilirubin biphasic illness presentation | Conjunctival suffusion, leukocytosis second phase of illness associated with fever hemorrhagic dengue infection typically manifests at the time the fever abates | Management of both illnesses requires careful monitoring of fluid and electrolyte balance, hemostasis, and/or intensive care for support of cardiovascular and respiratory failure |
| | Relapsing fever caused by *Borellia recurrentis* or related species | Fever, headache, myalgia, nausea, bleeding, vomiting, nonproductive cough, thrombocytopenia, abdominal pain, rash, conjunctival suffusion (rarely). Exposure to ticks or lice | Conjunctival suffusion, fever does not follow relapsing fever pattern, lack of exposure to ticks or lice | Oral doxycycline is used to treat either infection |
| | Viral hepatitis | Fever, nausea, vomiting, elevated | Conjunctival suffusion, thrombocytopenia | Infectious hepatitis is discussed in ► Chap. 13 |

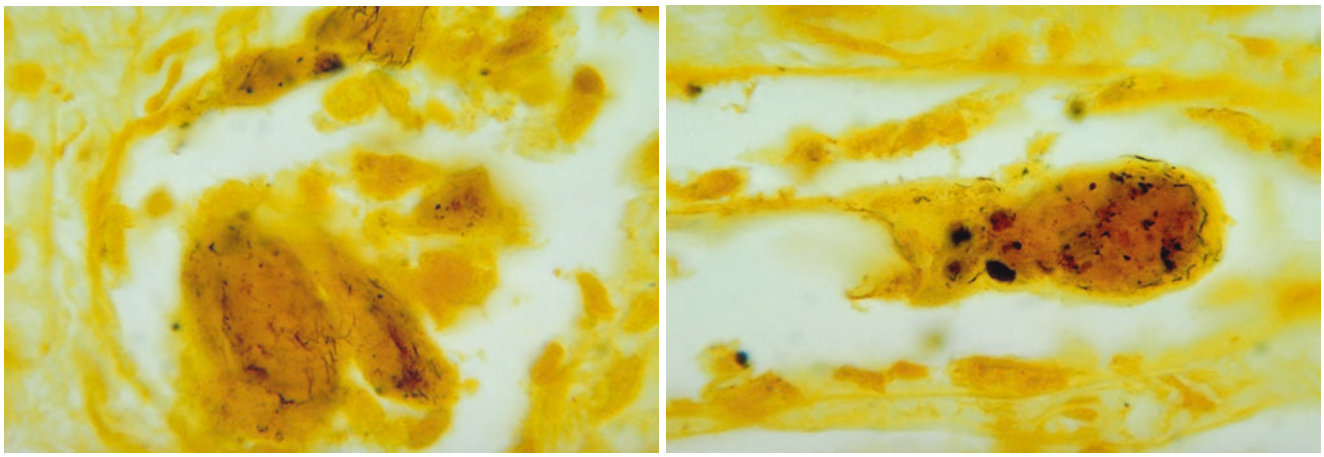

**Fig. 37.3** The hematogenous seeding of *Leptospira* species that occurs during the bacteremic phase of disease can lead to infection of many organs and tissues including the liver (*left panel*) and kidney (*right panel*) as seen here following silver staining. (Pictures were obtained from the CDC Public Health Image Library, credited to Dr. Martin Hicklin)

**Table 37.2** Abnormal laboratory findings seen in patients with leptospirosis

| | Abnormal findings |
|---|---|
| Complete blood count | Anemia, thrombocytopenia<br>Leukocytosis with neutrophil predominance<br>Leukopenia is seen in severe disease |
| Metabolic panel | Elevated bilirubin and hepatic transaminases<br>Elevated creatinine, blood urea nitrogen, low serum sodium |
| D-dimer | Elevated D-dimer in severe disease |
| Erythrocyte sedimentation rate | Elevated |
| Urinalysis | Hematuria, proteinuria, and pyuria<br>Granular casts may be observed |
| Electrocardiogram | PR prolongation<br>Atrial fibrillation |
| Chest radiograph | Highly variable depending on the severity of lung involvement |
| | Gulati et al. described "rapidly evolving, predominantly peripheral diffuse nodular or confluent pulmonary lesions" as typical of leptospirosis |
| | Chierukal noted that "nodular or patchy infiltration, sometimes with localized confluent consolidation," is typical of leptospirosis-associated pulmonary hemorrhage, while isolated interstitial infiltrate is uncommon |
| Cerebrospinal fluid | Consistent with aseptic meningitis, including an elevated opening pressure, normal glucose concentration, elevated protein concentration, and a lymphocytic pleocytosis |
| Renal biopsy | Acute tubulointerstitial nephritis, with primary injury of the proximal convoluted tubules |
| Liver biopsy | Variable, ranging from no involvement to hepatocellular necrosis |

**Call Out Box 37.3**

The **Jarisch-Herxheimer** phenomenon is an adverse reaction known to occur shortly after antibiotic treatment is initiated. The reaction includes an abrupt onset of high fever and chills that may be associated with renal or hepatic insufficiency and hypotension. Severe reactions are life threatening. **Jarisch-Herxheimer** reactions are classically associated with the use of penicillin to treat syphilis, but the treatment of other spirochete infections can trigger the same problem. Symptoms begin within 24 hours of starting treatment and can last for several days.

## 37.9 Treatment for Leptospirosis

Mild to moderate cases of leptospirosis, including the vast majority of those diagnosed during the leptospiremic phase, should be treated with oral doxycycline. Severe and complicated infection requires treatment with intravenous benzylpenicillin. Intensive care monitoring and supportive care may be necessary. A recognized complication that can occur during treatment for leptospirosis is the development of a Jarisch-Herxheimer reaction [▶ Call Out Box 37.3].

## 37.10 Exercises

Please refer to the supplementary information section for answers to these exercises.

1. A 47-year-old health-care worker presents to the ER with 2 days of fever and dry cough. He returned home from a 2-week trip to Puerto Rico 6 days ago. In Puerto Rico, he volunteered to assist in recovery efforts following Hurricane Irma. He reports fever and myalgias a few days before returning home. He states that he felt fine for the last 3 days, but woke up this morning with fever and cough. He also noticed that he was jaundiced and had developed a petechial rash on his lower extremities. On physical examination, his vital signs show a temperature of 39 °C, heart rate of

123 beats per minute, respiratory rate of 20 breaths per minute, and blood pressure of 100/70. He is icteric, has an enlarged liver 3 cm below the right costal margin, and a fine petechial rash on both lower extremities. You suspect leptospirosis and have just ordered the appropriate diagnostic tests including a microscopic agglutination test, blood polymerase chain reaction test, and blood and urine cultures. Results will not be available for several days. Of the following options, the best next steps in managing the patient include:

(a) Hospitalization, await definitive test results, provide aggressive supportive care
(b) Hospitalization, begin empiric intravenous benzylpenicillin, provide aggressive supportive care
(c) Request a chest radiograph, complete blood count, comprehensive metabolic panel, and coagulation studies, and advise the patient to return to the office the next day to review the test results
(d) Hospitalization, begin empiric oral amoxicillin, provide aggressive supportive care

2. A 29-year-old farmer from Barbados who is visiting family in Florida presents to your office with 3 days of fever, muscle pain in his calf, headache, and nausea. He arrived in Florida 10 days ago. It is the rainy season in Barbados. The patient explains that his 19-year-old sister and 51-year-old father who are both in Barbados have similar symptoms. The family maintains a large farm that includes sheep, goats, and cows. During the patient's physical examination, you observe an ocular finding that brings leptospirosis to the top of your differential diagnosis. What did you see?

(a) Anisocoria
(b) Uveitis
(c) Conjunctival suffusion
(d) *Leptospira* in the vitreous fluid

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# Leprosy

## A Chronic Skin Lesion that Feels Numb

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**Learning Objectives**

- Understand the challenges that contribute to the typical delay in diagnosing leprosy.
- Outline the risk factors for acquiring leprosy.
- Describe both the typical and atypical clinical presentations of leprosy.
- Differentiate leprosy from more common diseases with similar presentations.

## 38.1 Introduction

Leprosy, also known as Hansen's disease (HD) [▶ Call Out Box 38.1], is a chronic infection caused by the acid-fast bacillus, *Mycobacterium leprae*. During infection, *M. leprae* damages skin and skin structures, including peripheral nerves. The World Health Organization (WHO) classifies leprosy as a neglected tropical disease because the diagnosis is very frequently delayed until significant tissue destruction has occurred. Milder forms of the infection may never be diagnosed. The complex social and cultural history of leprosy offers a unique layer of challenge to making the diagnosis. Moreover, most physicians are unaware of the spectrum of clinical presentations and pathological findings of leprosy, and since several more common diseases present in a similar manner, those illnesses are usually considered first.

Untreated, lepromatous leprosy leads to significant, often irreversible nerve damage and subsequent disability and deformity. Lepromatous and tuberculoid diseases are best treated with different antibiotic regimens; thus, it is important to understand where a patient falls along the spectrum of illness in order to best inform proper antibiotic treatment.

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## 38.2 Epidemiology of Leprosy

Globally, between 200,000 and 300,000 people are infected every year with *M. leprae*. In 2015, more than 100 nations reported new cases of leprosy to the WHO; however people living in India, Brazil, and Indonesia accounted for more than 80% of new cases. Clearly, the infection is widespread with well-defined pockets of the highest disease activity. Historically, individuals with leprosy have faced intense stigma and marginalization, due at least in part to false beliefs regarding transmission of the disease and its association with poor hygiene and severe poverty. Although millions of cases of leprosy have been cured since the highly effective three-drug antibiotic treatment regimen was first recommended in 1981, the disease persists.

In the *United States*, approximately 6,500 people are currently diagnosed with leprosy. According to Health Resources and Services Administration (HRSA) of the US Department of Health & Services, there were 178 new cases of leprosy reported from 31 states and Puerto Rico in 2015. Over 70% of these registered cases were reported from Florida, California, New York, Louisiana, Texas, and Hawaii. Recent reports of increasing disease prevalence in the Southern United States underscore the importance of recognizing leprosy as a public health concern in the United States. Furthermore, while some cases of leprosy reported in the United States may be linked to time spent outside of the country, increasing evidence supports the persistence of indigenous disease [▶ Call Out Box 38.2].

**Call Out Box 38.1**
The word leprosy is derived from the ancient Greek term for "a disease that makes the skin scaly." In 1873, the Norwegian physician and epidemiologist **Gerhard Henrik Armauer Hansen** identified *Mycobacterium leprae* as the cause of leprosy.

**Call Out Box 38.2**
In 2015, more than 65% of newly reported leprosy cases were of people who had never traveled outside of the United States. Leprosy remains endemic to parts of the United States, but not because of human to human transmission. The primary vector for the ongoing indigenous transmission of leprosy in the United States is the wild armadillo.

## 38.3 Transmission

Leprosy affects both males and females of all age groups. The incubation period of *M. leprae* is highly variable. The WHO reports an average incubation period of 5 years, but it has been reported to range from less than 3 to more than 20 years. Hence, the disease can take years to manifest in humans. Most people who are exposed to *M. leprae* do not become infected. The mechanism of leprosy transmission is not fully understood. Human-to-human transmission is uncommon and requires very close contact. Zoonotic transmission, especially from handling armadillos or consuming armadillo meat, is increasingly recognized.

### 38.3.1 Human-to-Human Transmission of *M. leprae*

Leprosy can be transmitted from close and frequent contact with infected, untreated individuals. The bacterium is spread via *respiratory droplets* from the nose and mouth. Evidence for viable *M. leprae* in the desquamating epithelium of leprosy patients is not very convincing; however, the skin has also been reported as a possible mode of transmission. Patients who have traveled to areas with relatively increased prevalence of leprosy may be at increased risk for infection with *M. leprae*, but the infection is *not* highly contagious between humans. Although incidence rates are

**Call Out Box 38.3**
The majority of people who develop leprosy have no known history of contact with an infected individual.

higher for those with prolonged, close contact with affected individuals when compared to the general population, most exposed individuals will not develop leprosy [▶ Call Out Box 38.3].

### 38.3.2 Zoonotic Transmission of Leprosy from the Nine–Banded Armadillo

The zoonotic transmission of leprosy has gained increasing attention in recent years, especially in the Americas. Direct or indirect exposure to the nine-banded armadillo, *Dasypus novemcinctus*, is recognized as a significant risk factor for disease transmission. Thus, it is important for clinicians to consider including leprosy in the differential diagnosis of patients presenting with dermatological manifestations if they live in or travel to areas known to be endemic to wild armadillos.

## 38.4 Diagnosing and Classifying Leprosy

The diagnosis of leprosy is most often made based on its clinical characteristics and the presence of three cardinal signs: hypopigmented or erythematous skin lesions with a definite loss of sensation; the presence of enlarged, impaired nerves at characteristic sites; and identification of acid-fast bacilli on slit-skin samples [▶ Call Out Box 38.4].

The hypopigmented or erythematous skin lesions can be macular, nodular, or plaque-like and may be present in patches. They may be located anywhere on the body, but the cooler areas of the face and the extensor surfaces of the extremities are most common because *M. leprae* grows best at lower temperatures. Sensory loss is best determined by pinprick testing of the affected area.

The nerves supplying the area with the lesion(s) should be palpated for tenderness or enlargement. Loss of skin sensation and/or findings of muscle weakness in the areas supplied by the nerve are not uncommon. Because the earlobes are very frequently involved, they should be examined for signs of thickening or presence of nodules.

Slit-skin samples are collected from small cuts in the skin for acid-fast staining. Sampling should include the area(s) of the skin lesion(s) and one or both ear lobes, even if they do not appear to be affected. Up to four slit-skin sampling sites are recommended [▶ Call Out Box 38.5].

In addition to the *three cardinal signs of leprosy*, it is important to recognize that the manifestations of infection have a wide range of possible clinical and pathological presentations. The range of dermatologic manifestations of disease from tuberculoid to lepromatous leprosy is summarized in [1].

**Call Out Box 38.4**
There are **three** cardinal signs of leprosy:
1. Hypopigmented or erythematous skin lesions with a definite loss of sensation
2. The presence of enlarged, impaired nerves at characteristic anatomic sites
3. Identification of acid-fast bacilli on slit-skin samples

**Call Out Box 38.5**
**The absence of the cardinal signs of leprosy *does not rule out the diagnosis*.** While a positive slit-skin smear test is diagnostic, most patients with leprosy will have negative test results. A full-thickness skin biopsy of the most active part of the lesion may confirm diagnosis if suspicion remains high. Scrapings and biopsies of lower temperature skin areas are also recommended. If a nerve biopsy is warranted, a thickened cutaneous nerve is the preferred target.

The WHO recommended treatment regimen for the disease is dependent on whether the patient's findings more closely match the paucibacillary (PB) or multibacillary (MB) state. Given the wide range of variability in the skin findings, classification can be quite challenging.

Tuberculoid leprosy is associated with a good prognosis. The lesions often heal on their own (◘ Figs 38.1 and 38.2). Lepromatous leprosy can progress very slowly and take years to be accurately diagnosed. Alopecia is noted frequently, particularly of the eyelashes and eyebrows. As the infection advances, the nasal mucosa is quite often involved leading to severe disfiguring and disabling tissue destruction (◘ Fig. 38.3).

### 38.4.1 Additional, Classifications of Leprosy

A diagnosis of *indeterminate leprosy* is considered when the histopathology of the earliest skin lesion exhibits chronic, nonspecific inflammation with infiltration of lymphocytes and histiocytes. Careful microscopic inspection reveals involvement of fine dermal nerves including the presence of an inflammatory infiltrate around the perineurium. Very few acid-fast bacilli are present, if at all. Clinically, indeterminate leprosy presents as faint, hypopigmented, or erythematous macules, usually on the extremities. This very early stage of leprosy may resolve spontaneously, or it may progress to any one of the five forms described in ◘ Table 38.1. Indeterminate leprosy may persist for several months before resolving or progressing–depending on the host's cellular immune response to the infection.

*Pure neural leprosy (PNL)* is a particular challenge to diagnose since, as the name suggests, the infection spares the skin and is localized to the nerves. PNL accounts for at least 5% of cases, with higher rates being observed in some

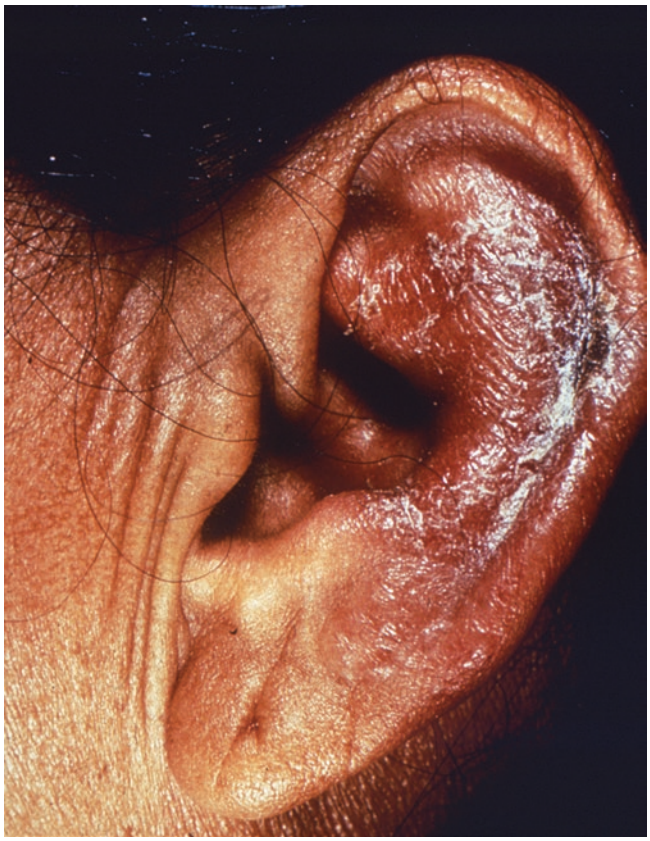

**Fig. 38.1** Shown is an inflammatory lesion on the pinna of the left ear. A full-thickness skin biopsy confirmed the suspected diagnosis of tuberculoid (paucibacillary) leprosy. *Earlobes are the most frequently affected area of the body.* (Photo source: CDC/Arthur E. Kaye)

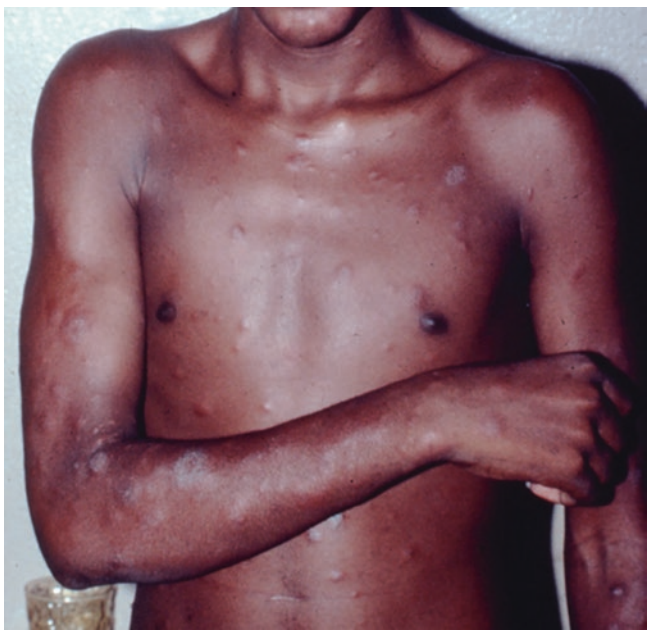

**Fig. 38.2** Multiple skin lesions in a man with tuberculoid (paucibacillary) leprosy. (Image provided by Dr. Joseph Domachowske)

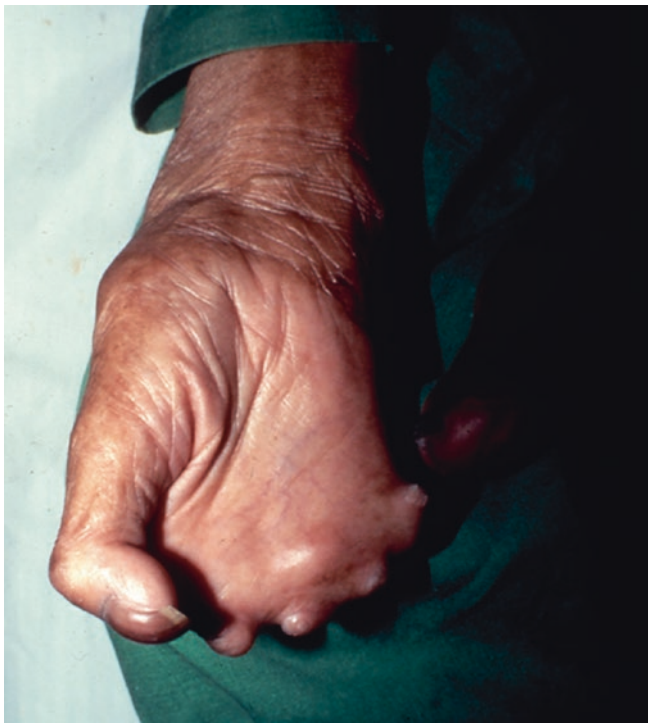

**Fig. 38.3** Shown is the right hand of a man with an advanced and disfiguring case of lepromatous (multibacillary) leprosy. His left hand was similarly disfigured, and he had extensive tissue loss of his nose, nasal mucosa, and parts of his face. This infection likely began decades earlier. He was never treated for the disease. (Image provided by Dr. Joseph Domachowske)

38

regions of higher disease incidence, such as India. Clinically, PNL presents as axonal nerve impairment and thickening, with or without tenderness or pain, in the absence of skin lesions. Histopathologic findings are usually nonspecific, and if acid-fast organisms are not observed in nerve biopsy material, polymerase chain reaction-based testing can be performed on nerve biopsy material in an attempt to identify the presence of *M. leprae*-specific DNA.

### 38.4.2 The Differential Diagnosis for the Signs and Symptoms Typically Seen in Leprosy

The extensive range of skin manifestations that may be seen during *M. leprae* infection brings with it a long list of other diagnostic possibilities, many of which are far more common than leprosy. Examples of such dermatologic disorders, and the features that they share with *M. leprae* infection, are listed in Table 38.2.

Since skin findings from leprosy can be so variable, it's difficult to exclude the diagnosis based on appearance alone. One feature that essentially eliminates *M. leprae* as a diag-

**Table 38.1** Classifications of leprosy based on clinical and histopathologic findings from the skin lesions

| WHO classification | Paucibacillary | | Multibacillary | | |
|---|---|---|---|---|---|
| HRSA[a] classification | *Tuberculoid leprosy* | *Borderline tuberculoid* | *Borderline-borderline* | *Borderline-lepromatous* | *Lepromatous leprosy* |
| *Quantity of lesions* | Five or fewer (often one) | Variable | | | Six or more |
| *Shape/size* | Macules or plaques, asymmetrical with well-defined edges, less than 10 cm before self-healing | Variable, plaques are larger with satellite lesions | Macular, papular, and/or plaque like, may be annular in shape | Symmetrical macular lesions, well-defined nodular areas | Macules with *poorly defined* margins; advanced infection associated with nodules and/or plaques |
| *Color* | Hypopigmented or red | Variable | | | Skin-colored or red. Variations present with advanced disease |
| *Sensation* | Definite loss of sensation; thickened cutaneous nerves may be palpated around lesion | Variable | | Less likely to have severe sensory loss | |
| *Location* | Anywhere | Tend to involve a larger part of extremities or trunk | Variable | Symmetrical distribution | |
| *Acid-fast smear from slit-skin samples* | Negative | Variable | | Positive | |
| *Histological appearance* | Epithelioid noncaseating granulomas | Mixed | | Foamy macrophages and histiocytes | |

[a]Health Resources and Services Administration, US Department of Health and Human Services

nostic possibility is the presence of pruritis. Itching can be quite intense from a variety of skin diseases, including many of the disorders listed in Table 38.2, helping to narrow one's differential diagnosis away from leprosy as a possibility [► Call Out Box 38.6]. Additional features that generally support the diagnosis of leprosy over other diagnoses that share similar features include the presence of a chronic rash that is unresponsive to usual topical treatments; a loss of sensation at the site of the lesion; lesions localized to the digits, earlobes, face, or extensor surface of the extremities; thickened or nodular earlobes; alopecia, particularly of eyelashes and eyebrows; nasal mucous membrane involvement; a history of travel to a high prevalence area or direct and frequent close contact with someone known to have leprosy; and direct exposure to wild armadillos or consumption of armadillo meat.

## 38.5 Treatment of Leprosy

To determine the most appropriate treatment regimen for a given patient, it is first necessary to determine whether the patient's infection more closely resembles the tuberculoid or lepromatous form of the disease (Table 38.1). General guidelines for the treatment of tuberculoid (paucibacillary) leprosy indicate the two-drug regimen of dapsone and rifampin for a period of 6 months. In contrast, lepromatous (multibacillary) disease is treated with the three-drug regimen of dapsone, rifampin, and clofazimine for a period of 2–5 years. Adjunctive therapy with systemic glucocorticoids may ameliorate or prevent nerve involvement. Nerve damage that has been present for more than 6 months is unlikely to respond to adjunctive glucocorticoid therapy. In circumstances where the specific form of leprosy remains unclear

**Table 38.2** Dermatologic disorders that share features with *Mycobacterium leprae* infection

| Dermatologic disorder | General type of disorder | Features shared with *M. leprae* infection |
|---|---|---|
| Psoriasis vulgaris | Autoimmune inflammatory disorder | Presence of inflammatory plaques |
| Pityriasis rosea | Dermatosis | Herald patch with symmetrical eruption lasting up to several months |
| Vitiligo | Autoimmune depigmentation disorder | Hypopigmentation |
| Contact dermatitis | Allergic inflammation | Presence of inflammatory macules |
| Atopic dermatitis | Allergic inflammation | Presence of inflammatory plaques, hypopigmentation |
| Cutaneous leishmaniasis | Parasitic infection | Chronic raised, scaly inflammatory lesions |
| Mycosis fungoides | A form of cutaneous T-cell lymphoma | Presence of red, scaly patches |
| Tinea versicolor | Superficial fungal infection | Hypopigmentation |
| Subacute cutaneous systemic lupus erythematosus | Autoimmune inflammatory disorder | Presence of inflammatory scaly plaques |

**Call Out Box 38.6**
Images highlighting dermatologic presentations of *M. leprae* infection and comparisons to common misdiagnoses, such as those listed in Table 38.2, can be found in the International Textbook of Leprosy at: ► http://www.internationaltextbookofleprosy.org/chapter/differential-diagnosis-leprosy

after the evaluation is complete, patients should be treated with the three-drug regimen. Doing so increases the chances for an optimal outcome and reduces the potential for the organism to develop resistance over time. Antibiotics needed for the treatment of leprosy in many parts of the world are provided free of charge by the World Health Organization. In the United States, disease surveillance is tracked and reported by the *National Hansen's Disease Program (NHDP)*. The organization also provides guidance on the treatment of leprosy and how to best gain access to the necessary medications.

## 38.6 Reactions During or After Antibiotic Treatment for Leprosy

Leprosy reactions may arise during or following successful antibiotic treatment and can be a major cause of morbidity if not recognized and treated in a timely fashion. Patients who are being treated for leprosy, as well as the clinicians who are prescribing the antibiotics, must be aware that treatment emergent inflammatory reactions are potentially serious complications of the therapeutic regimen.

*Type 1 leprosy reactions* occur predominately during the treatment of borderline forms of leprosy. These type-4 delayed hypersensitivity reactions present suddenly with redness, swelling, and warmth of the preexisting leprosy lesions. The reaction occurs most commonly during the first months of treatment. Other signs of a type 1 leprosy reaction include generalized edema and sensory nerve deficits. Treatment with systemic glucocorticoids is indicated.

*Type 2 leprosy reactions* present as erythema nodosum leprosum *(ENL)*. This phenomenon occurs in approximately half of the patients undergoing treatment for lepromatous leprosy, usually sometime during the first 3 years of therapy. The ENL nodular skin lesions may ulcerate or become pustular during more severe reactions. A systemic inflammatory response characterized by fever, malaise, and tachycardia may develop. Type 2 leprosy reactions vary in severity and duration from one patient to the next. Adjunctive treatment with systemic glucocorticoids is indicated.

## 38.7 Exercises

Please refer to the supplementary information section for answers to these exercises.

? 1. A 32 year old man complains of multiple erythematous lesions on his elbows, hands, and feet. He explains that the lesions have worsened during colder weather, but that they do not cause him any pain or discomfort. On physical examination, skin lesions are present in the areas he described. They are different sizes and shapes, dull red in color and appear plaque-like. Of the following, the finding that is least consistent with a diagnosis of leprosy is the:
   A. Presence of scratch marks along the skin lesions.
   B. Lack of pin prick sensation at the location of the rash.
   C. Swollen, nodular earlobes.
   D. Dull red color of the lesions.

? 2. A 25-year-old patient returns for routine follow-up during his treatment for leprosy, but mentions that he's not been feeling well for the last 2 weeks. His only complaint is a feeling of general malaise. His vital signs show a temperature of 38.1 °C and a heart rate of 124 beats per minute. His current medications include dapsone, rifampin, and clofazimine, all of

which he has been taking for the last 5 mos to treat multibacillary leprosy present on both hands. Of the following options, the best approach to the patient's newest complaint is to:

A. Continue the current antibiotic regimen, offer supportive care for pain and fever, and begin a diagnostic evaluation to identify the source of the patient's fever and malaise.
B. Reassure the patient that this reaction occurs in many patients taking medication for the treatment of leprosy, and the symptoms should improve with time.
C. Continue the current antibiotic regimen, and begin a course of systemic glucocorticoid therapy.
D. Instruct the patient to stop taking the current antibiotic regimen and prescribe an alternative.

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# Neurocysticercosis

## First Time Seizure in a Recent Immigrant From Mexico

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**Learning Objectives**

- Review the life cycle of the pork tapeworm, *Taenia solium*.
- Describe the usual routes of transmission of *Taenia solium* to humans.
- List the clinical manifestations of neurocysticercosis.

## 39.1 Introduction

Globally, neurocysticercosis is the most common parasitic infection of the central nervous system [1]. Although the disease is endemic to tropical zones of the Americas, Asia, and Africa, it is also emerging as an important infection in the United States among immigrants from disease-endemic regions and among international travelers. The US Centers for Disease Control and Prevention has identified neurocysticercosis as one of five neglected parasitic infections [1]. These infections are considered neglected because relatively few resources have been allocated to their surveillance, prevention, and/or treatment [▶ Call Out Box 39.1].

Neurocysticercosis is a subtype of cysticercosis caused by the pork tapeworm, *Taenia solium*, during its larval stage. *Extraneural cysticercosis* is used to describe the parasitic infection when it occurs outside of the central nervous system. Cysticercosis can affect a range of different tissues and organs, but the organism's greatest tropism is for muscle and subcutaneous tissue [2]. Muscle and soft tissue cysticercosis is usually only an aesthetic burden as it seldom confers significant pathology at these sites [1, 2]. Infection of the central nervous system is referred to as *neurocysticercosis*, an illness that can be further divided into *parenchymal* and *extraparenchymal* types. *Extraparenchymal neurocysticercosis* occurs in the central nervous system, but does not involve the brain parenchyma proper. Anatomical areas such as the spinal cord, the subarachnoid space, the ventricular system, and the ocular bulb may be involved. Infection leads to the formation of cystic changes in the tissue. Extraparenchymal cysts are usually larger than parenchymal cysts due to lack of physical inhibition by the brain parenchyma. Infections within the central nervous system, but not involving the brain itself, have a wide range of clinical presentations, largely characterized by the anatomic location(s) of the cyst(s) themselves. Non-communicating hydrocephalus is not unusual. *Parenchymal neurocysticercosis*, the most common form of cysticercosis, typically presents as new-onset seizures [1, 2].

**Call Out Box 39.1**
The five neglected parasitic diseases identified by US Centers for Disease Control and Prevention are American trypanosomiasis (Chagas disease), cysticercosis, toxocariasis, toxoplasmosis, and trichomoniasis.

## 39.2 Transmission of *Taenia solium*

*Taenia solium* is one of several tapeworms (cestodes) that infect humans [▶ Call Out Box 39.2]. The life cycle of *Taenia solium* is maintained between pigs, serving as the parasite's intermediate host, and humans, serving as the definitive host [3]. It is through this life cycle that *Taenia solium* causes *taeniasis*, a generally benign adult tapeworm infection of the human gastrointestinal tract [3]. *Taeniasis* occurs after ingestion of a sexually mature tapeworm that remains in the human intestinal tract and cannot disseminate to other tissues. ◘ Figure 39.1 illustrates how cysticercosis occurs during a break in this cycle when a human ingests eggs or a gravid proglottid (◘ Fig. 39.2). The gastric environments of pigs and humans are similar, so in this circumstance, the tapeworm's life cycle continues in the human just as it would in the pig, ultimately leading to the emergence of oncospheres that are able to migrate to the tissues and form cysticerci.

## 39.3 Definitions

**Neurocysticercosis** - Infection of the central nervous system by the pork tapeworm, *Taenia solium*.

**Taeniasis** - Infection of the gastrointestinal tract by *T. solium* (or *T. saginata*, the beef tapeworm).

**Oncosphere** - The larval stage of a tapeworm that emerges after eggs are ingested by an intermediate host.

**Cysticercus** - The larval stage of a tapeworm when the scolex is inverted into a sac. During this stage, the parasite is often encysted within the muscle tissue of the host. In the case of neurocysticercosis, the cysticerci are found within the central nervous system.

**Proglottid** - A segment of the adult tapeworm containing a sexually mature reproductive system.

**Intermediate host** - An organism that harbors the sexually immature form of a parasite for a brief period before transfer to the definitive host.

**Definitive host** - An organism that harbors the sexually mature stage of a parasite.

## 39.4 Clinical Features of Neurocysticercosis

Cysticerci become pathologic when they develop in anatomical areas where small physical disturbances cause profound pathology [1, 2]. This is most often observed in the central nervous system (neurocysticercosis) but can be seen in the ocular system and, very rarely, in or around the conduction system of cardiac tissue [2].

**Call Out Box 39.2**
Tapeworms (cestodes) that regularly cause disease in humans include *Taenia solium* (pork tapeworm), *Taenia saginata* (beef tapeworm), *Diphyllobothrium latum* (fish tapeworm), *Hymenolepis nana* (dwarf tapeworm), *Echinococcus granulosus* (dog tapeworm), and *Dipylidium caninum* (puppy tapeworm).

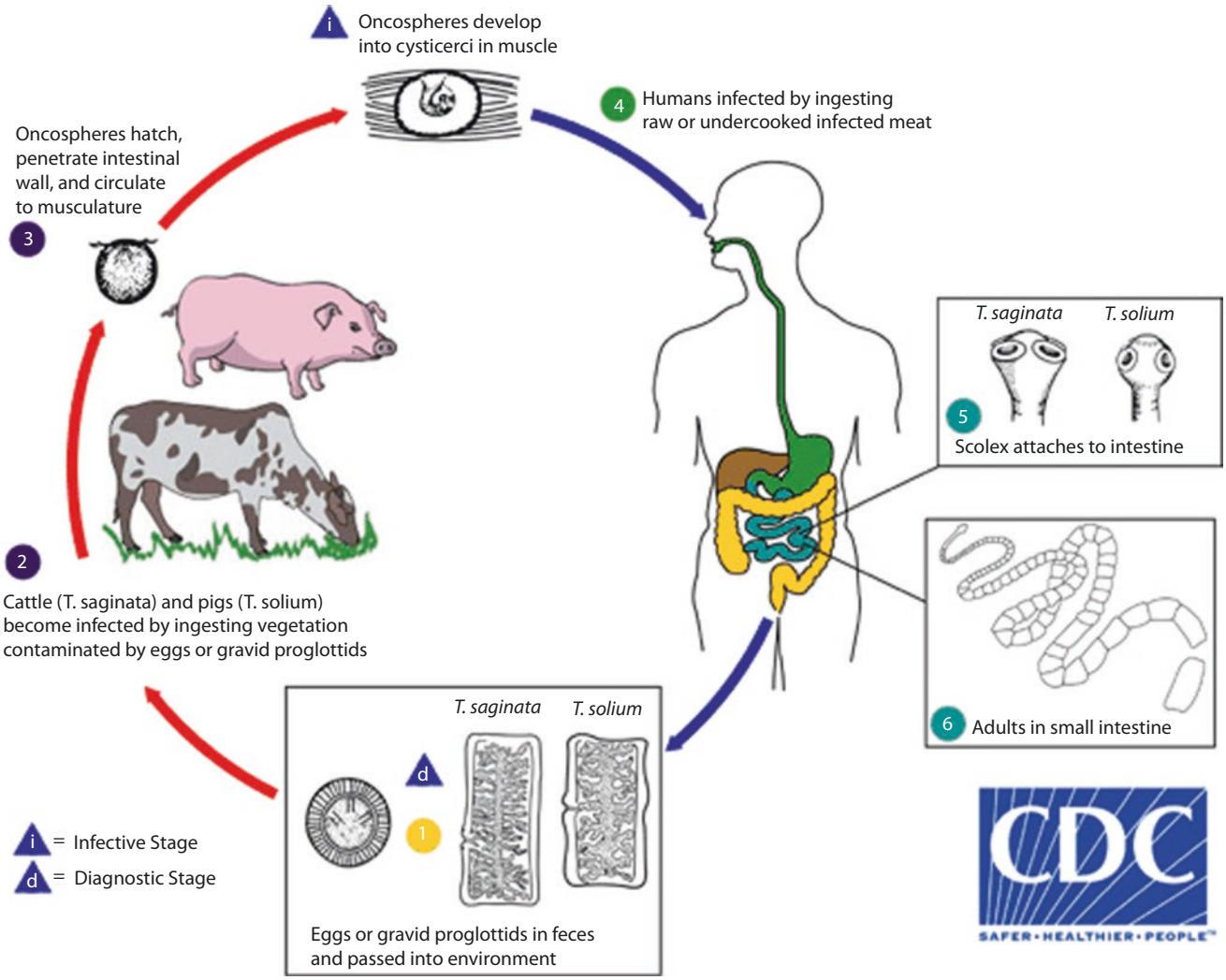



**Fig. 39.1** The life cycle of *T. solium* begins when eggs are introduced into the environment by way of human feces (1). A pig consumes vegetation contaminated with these eggs (2). The acidic conditions in the stomach of the pig will stimulate the eggs to hatch. The larval oncospheres penetrate the pig's intestinal mucosa and migrate via lymphatics or blood vessels to the muscles or other tissues of the animal (3). In the muscle tissue, the oncospheres develop into cysticerci. Humans consume improperly cooked pork containing the cysticerci (4). The head of the now mature worm envaginates upon entry into the small intestine and tethers to its wall (5). The tapeworm then sheds proglottid throughout its life in the intestine (6). This infestation is referred to as *taeniasis* and is often asymptomatic conferring minimal morbidity. If gravid proglottid is released into the environment, the individual with *taeniasis* can autoinoculate themselves with tapeworm eggs via the fecal oral route. Eggs hatch in the acidic environment of the human stomach. The emerging oncospheres (larvae) can now penetrate the intestinal wall and cause systemic disease, including neurocysticercosis. (Image credit: CDC [3])

Although neurocysticercosis has a high pathological potential, most cases are clinically silent. Autopsies performed on individuals from endemic areas show incidental neurocystocerci in nearly 2% of the population [▶ Call Out Box 39.3] [5].

When neurocysticercosis does present clinically, the most common symptom is an abrupt onset of seizures [▶ Call Out Box 39.4] [5]. Approximately 30% of late-onset epilepsy occurring in individuals living in endemic regions is attributed to neurocysticercosis [1]. Seizures are a manifestation of parenchymal neurocysticercosis, an infection that is generally associated with a very good prognosis. Although seizures are the most common clinical feature of parenchymal neurocysticercosis, the disease can present with a diverse set of symptoms ranging from psychiatric

**Call Out Box 39.3**
Globally, neurocysticercosis causes an estimated 50,000 deaths per year.

**Call Out Box 39.4**
Neurocysticercosis should be included in the differential diagnosis for any patient presenting with *new-onset seizures* who is from or has traveled to an *endemic region*.

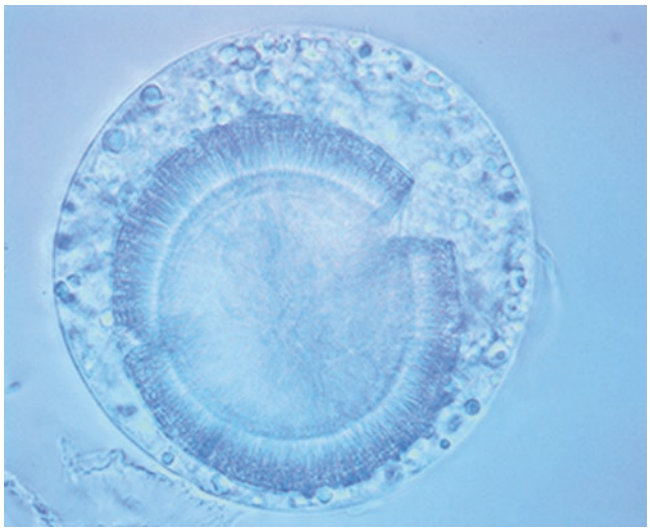


**Fig. 39.2** Wet mount microscopic image of a *Taenia* species egg under oil immersion (1000×). It is not possible to differentiate *T. solium* eggs from *T. saginata* (beef tapeworm) eggs microscopically. (Image kindly provided by Dr. Scott Ridell)

issues to compromised cognition [1]. The wide range of potential neurologic and neuropsychiatric symptoms are largely dependent on the specific anatomic location(s) of the cysts. Upon physical examination of any patient with a history of travel to or emigration from an endemic region presenting with seizures and/or new neurological pathology, neurocysticercosis should be considered.

Extraparenchymal neurocysticercosis has a more varied clinical presentation and is associated with a poor prognosis. Extraparenchymal infection is less common than parenchymal disease, typically occurring in the subarachnoid space, within the ventricles, near the olfactory bulb, or in the meninges [1]. The meningeal form of cysticercosis presents with meningitis, with or without obstructive hydrocephalus. Associated clinical findings may induce diplopia, extraocular muscle paralysis, and other manifestations of cranial nerve palsies. Visual field deficits and other focal neurological deficits have also been described. The intraventricular and subarachnoid forms of cysticercosis present with increased intracranial pressure with the potential for tonsillar herniation [1, 2].

Cysticercosis present outside of the central nervous system is frequently asymptomatic. The patient may have cosmetic concerns from the appearance of the subcutaneous cysts, but these lesions confer little or no significant pathology or disability.

Neuroimaging findings with supporting serologic evidence is the most effective way to diagnose neurocysticercosis (Fig. 39.3) [▶ Call Out Box 39.5] [1, 5].

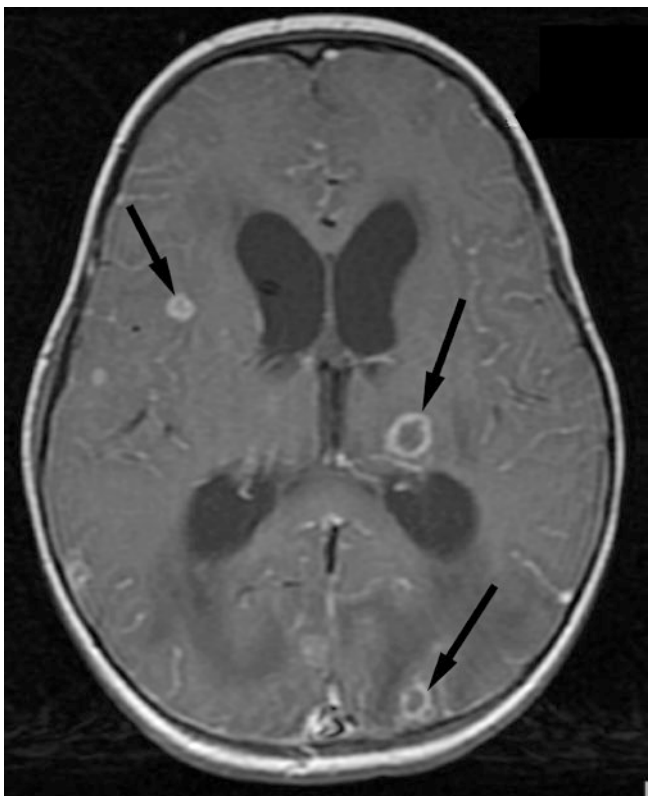


**Fig. 39.3** Magnetic resonance image of the brain of a 14-year-old Mexican boy with new-onset generalized seizures. Arrows highlight the presence of cystic lesions. Serologic testing confirmed the diagnosis of neurocysticercosis. (Image kindly provided by Dr. Joseph Domachowske)

**Call Out Box 39.5**

Taeniasis is acquired upon ingestion of *T. solium* cysticerci present in the muscle of improperly cooked pork.

Cysticercosis is acquired upon ingestion of *T. solium* eggs from contaminated food or via the fecal oral route, as occurs with autoinoculation.

39

**Case Study**

**Clinical Cases**

**Case 1**

A 63-year-old woman presents to the emergency department with dizziness after four focal tonic-clonic seizures of her left upper extremity, each lasting less than 10 min. She explains that "they always involve her arm and haven't changed much in the past 8 years." Social history reveals that the patient is an immigrant from Ecuador and visits her family in the United States for several weeks each year. Her physical examination is normal, including the absence of any focal neurological findings. A computer tomography scan of her brain shows three cystic lesions in the right frontal lobe. She underwent a stereotactic biopsy of one of the lesions because of concerns for malignancy. Histological examination revealed findings consistent with neurocysticercosis (Fig. 39.4). The patient was treated with a short course of the antiparasitic medication albendazole along with systemic dexamethasone and

given phenytoin to help prevent seizures. A follow-up computer tomography scan of her brain performed 3 months later revealed complete resolution of the lesions. After 6 months of being seizure free, the phenytoin was discontinued.

**Case 2**

A 29-year-old medical student presented to medical care after a single generalized tonic-clonic seizure that lasted approximately 12 min. Her past medical history included migraine headaches. This was her first seizure. A detailed history revealed that the patient had returned from a 10-week trip to Thailand 3 months ago. Her physical examination was unremarkable, including the absence of focal neurologic findings. A computer tomography scan of her brain revealed a single cystic lesion in the posteromedial right temporal region with surrounding edema. Neurocysticercosis was suspected given the patient's travel history and clinical presentation. The anatomic location of the cyst precluded surgical intervention or biopsy. The patient was treated empirically with albendazole and dexamethasone. Carbamazepine was administered for seizure control. A follow-up computer tomography scan of her brain was performed 4 months later revealing near-complete resolution of the lesion with a small residual calcification.

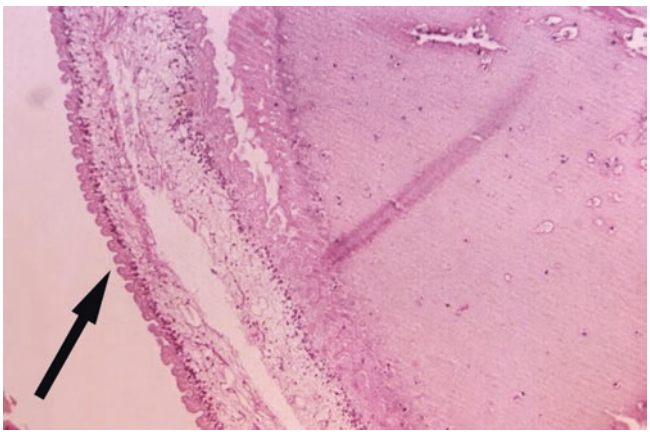


**Fig. 39.4** Cysticercus as seen in a brain biopsy specimen. The arrow points to the microvilli lining the outer layer of the cyst (100× magnification). (Image credit: Public Health Image Library [4])

## 39.5 Treatment of Neurocysticercosis

Initial treatment should focus on providing relief of the clinical manifestations of the infection. Increased intracranial pressure may require emergency surgery to relieve obstruction of cerebrospinal fluid flow. Patients with parenchymal neurocysticercosis may require anticonvulsant therapy for treatment or prevention of seizures. Subsequently, antiparasitic medication with or without concomitant systemic glucocorticoids should be considered depending on the state of the disease.

I. **Antiepileptic medication** should be considered for patients who present with seizures and for those who are at high risk for developing seizures. The presence of a large number of parenchymal lesions, evidence of pericystic inflammation, or findings consistent with cyst degeneration confer a high risk for the development of seizures. Phenytoin and carbamazepine are the most commonly used antiepileptic medications in the treatment or prevention of seizures secondary to neurocysticercosis [5].

II. **Antiparasitic therapy**: Antiparasitic therapy accelerates the resolution of active cysts and decreases the risk for developing hydrocephalus (extraparenchymal) and seizures (parenchymal). Albendazole is the medication of choice [1].

III. **Systemic glucocorticoids**: Cysticidal antiparasitic drugs, such as albendazole, can cause rapid tapeworm antigen release from the damaged parasites thereby triggering a robust inflammatory response. This inflammatory response can be associated with edema leading to an acute decompensation of the patient. Glucocorticoids are often used [1].

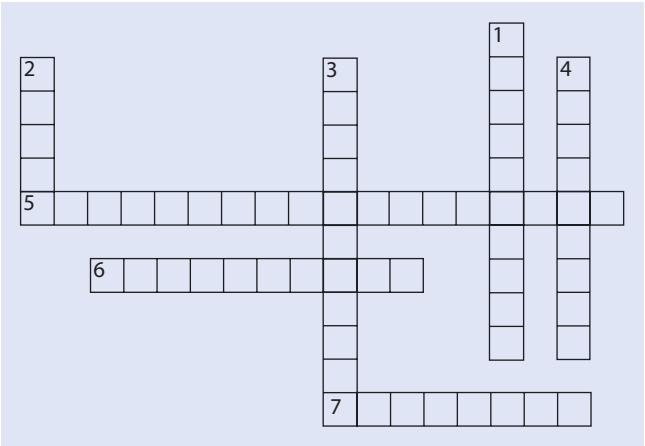
## 39.6 Exercises

Please refer to the supplementary information section for answers to these exercises.

1. Which of the following clinical scenarios should NCC be included on the differential (multiple answer choices)?
   a. A 13-year-old boy who emigrated from Colombia presenting with cranial nerve palsy and diplopia.
   b. A 40-year-old woman who has no recent travel history other than a vacation to Cancun 7 years prior and is now presenting with migraine headaches.
   c. A 64-year-old male who was diagnosed with taeniasis a month prior after persistent dyspepsia and non-bilious emesis. The patient now presents with focal headaches and vision problems.
   d. A 33-year-old man presenting with a sudden onset of tonic-clonic seizures. The patient only speaks Spanish so his history is unknown.

2. By which of the following methods is neurocysticercosis not transmitted to a human host?
   a. Human ingestion of undercooked pork.
   b. Autoinoculation in a patient who already has taeniasis.
   c. Human ingestion of cabbage handled by a person with taeniasis.
   d. Human ingestion of cabbage handled by a person with extraparenchymal neurocysticercosis but not taeniasis.
   e. Both a and c are acceptable choices.

3. Crossword




**Down**

1. A segment of the adult tapeworm containing a sexually mature reproductive system.
2. The true definitive host of *T. solium.*
3. The larval stage of a tapeworm when the scolex is inverted into a sac. In this stage, the parasite is often encysted within the muscle tissue of the host. In the case of neurocysticercosis, the cysticerci are found within the central nervous system.
4. Infection of the gastrointestinal tract by *T. solium*.

**Across**

5. Infection of the central nervous system by *T. solium.*
6. The larval stage of a tapeworm after ingestion by an intermediate host.
7. The most common presentation of a patient with parenchymal neurocysticercosis.

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# Human Immune Deficiency Virus

Contents

# Human Immunodeficiency Virus I: History, Epidemiology, Transmission, and Pathogenesis

*Bradford Becken III, Ami Multani, Simi Padival, and Coleen K. Cunningham*




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**Learning Objectives**

- Understand the epidemiology of HIV and AIDS
- Recognize factors that influence the transmission of HIV
- Review the pathogenesis of HIV infection

## 40.1 Definitions

**Lentivirus** - Genus of Retrovirus that contains HIV-1 and HIV-2

**MSM** - men who have sex with men. These individuals may not classify themselves as homosexuals

**Retrovirus** - Enveloped positive stranded RNA virus that replicated through a DNA intermediate

## 40.2 Introduction

While research has shown that human immunodeficiency virus (HIV) may have been present in humans as early as the start of the twentieth century in the Democratic Republic of the Congo (formerly Zaire), the diagnosis remained out of the public eye for over half a century [1]. In the 1980s, that all changed. When acquired immunodeficiency syndrome (AIDS) was first described in 1981, acquisition of the disease was considered a death sentence. More than 30 million people worldwide are infected, with the largest number of infected individuals living in resource-poor areas of sub-Saharan Africa and South and South East Asia. Additionally, it is estimated that only half to two-thirds of people with HIV currently have access to treatment [2]. In the United States, an estimated 1,122,900 people were living with HIV in 2015, which includes an estimate of the number of people with HIV who do not yet know of their diagnosis. In 2016, the last full year for which statistics are available, 39,782 new cases of HIV were diagnosed in the United States [3]. Infection with human immunodeficiency virus (HIV) and its end stage, acquired immunodeficiency syndrome (AIDS), is one of the most challenging public health crises of modern times and one of the most disastrous examples of the emergence, transmission, and dissemination of a microbial genome.

## 40.3 Introduction to the Problem

On June 5, 1981, the case report of five homosexual men with *Pneumocystis carinii* pneumonia, ages 29 to 36 and from Los Angeles, was published in the Center for Disease Control's (CDC) *Morbidity and Mortality Weekly Report*. All five men also had prior or current cytomegalovirus (CMV) infection and mucosal candidiasis. Two died by the time the cases were reported. These cases occurred between October 1980 and May 1981 [4]. At the time, AIDS had not been described and HIV had not yet been discovered. What was clear was that five individuals without a known immune deficiency had contracted infections historically seen only in patients who were profoundly immune-suppressed.

The report ended as follows:

"All the above observations suggest the possibility of a cellular-immune dysfunction related to a common exposure that predisposes individuals to opportunistic infections such as pneumocystosis and candidiasis. Although the role of CMV infection in the pathogenesis of pneumocystosis remains unknown, the possibility of *P. carinii* infection must be carefully considered in a differential diagnosis for previously healthy homosexual males with dyspnea and pneumonia [4]."

Soon after the report from Los Angeles, similar reports from San Francisco, New York, and other cities were reported, and the CDC noted that there was an increase in requests for pentamidine, which is used to treat *Pneumocystis* infections. By late 1982, the CDC compiled a set of risk factors associated with the condition which had become known as AIDS. In 1983, two researchers working independently, Robert Gallo and Luc Montagnier, published research manuscripts in Science describing a retrovirus isolated from two patients suffering from AIDS. The virus that they described would go on to be named HIV [5, 6].

Despite having identified the causative pathogen, progress in terms of diagnosis and treatment was slow, and the stigma associated with the disease often lead to discrimination. The first screening test for antibodies to HIV was not approved by the Food and Drug Administration (FDA) until 1985 [7]. Until testing was available, contaminated blood products were unknowingly being provided to patients. Two of the most famous victims of HIV associated with blood transfusions were Arthur Ashe, a tennis player who is believed to have contracted HIV after receiving blood products during heart surgery in 1983, and Ryan White, who contracted HIV from factor VIII infusions required to treat his hemophilia A [8, 9]. A more specific Western blot was approved by the FDA in 1987, which was also the year the antiretroviral for HIV, zidovudine (AZT), was first approved [10]. Prior to the release of AZT, the treatment of HIV/AIDS was limited to the complications and opportunistic infections associated with the diagnosis.

## 40.4 Epidemiology of HIV/AIDS

### 40.4.1 Global Epidemiology

Globally, since the start of the HIV/AIDS epidemic, more than 78 million people have been infected, and approximately 35 million people have died from HIV infection. It is estimated that since 2010, there have been no declines in new HIV infections among adults and that every year since 2010, approximately 1.9 million adults become newly infected with HIV each year. By the end of 2015, there were 36.7 million people living with HIV worldwide, and as of June 2016, only 18.2 million HIV-infected people had routine access to antiretroviral therapy. Despite the global impact of HIV,

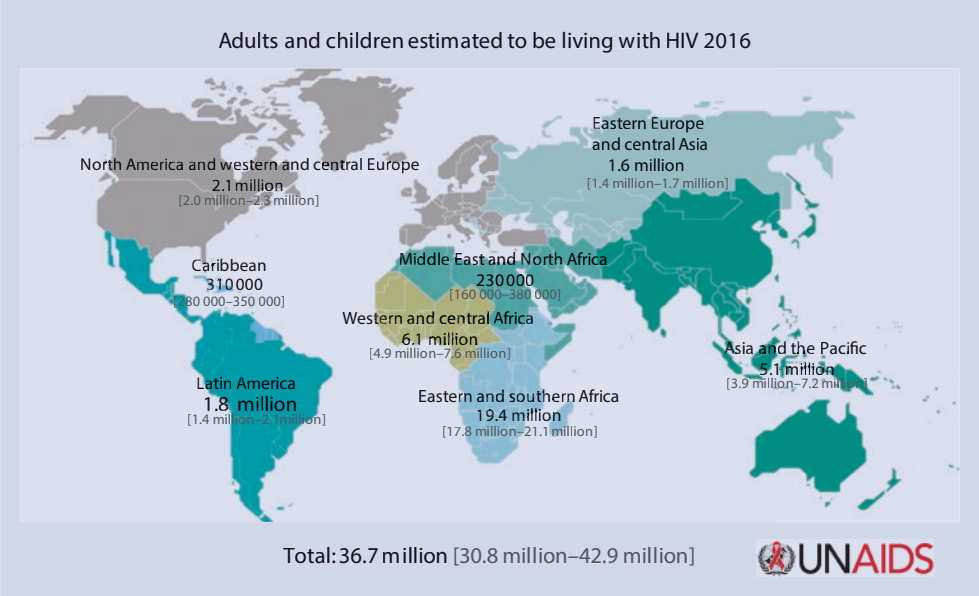


**Fig. 40.1** Global and regional estimated of adults and children living with HIV in 2016. (Reproduced from UNAIDS 2017 Core Epidemiology)

the burden of the epidemic varies significantly by geographic location, with eastern and southern Africa remaining the most severely affected (Fig. 40.1) [11].

### 40.4.2 US Epidemiology

In the United States in 2011, it was estimated that there were 1.2 million people living with HIV, 86% of whom were aware of their diagnosis, and 14% of whom were not [12]. Persons infected with HIV who are unaware of their status are responsible for nearly one-third of newly transmitted cases in the United States [13]. In 2015, 22% of all new HIV diagnoses in the United States were among persons aged 13–24 years, while those between the ages of 50 and 54 years accounted for the largest percentage of persons living with an HIV diagnosis (18%). With regard to race/ethnicity, the highest prevalence rates and highest rates of new HIV infection are found among African Americans, followed closely by Hispanics/Latinos. Although rates of new HIV acquisition are decreasing overall, gender remains a significant risk factor, with men accounting for 81% of all new HIV diagnoses reported in 2015. Seventy percent of new HIV infections are attributed to male-to-male sexual contact, 11% to injection drug use, 10% to heterosexual contact, 7% to male-to-male sexual contact *and* injection drug use, and 1% to perinatal transmission. Currently, the most at-risk group of individuals for new HIV infection includes young Black/African American and Hispanic/Latino gay and bisexual males. Many programs continue to put forth efforts to improve awareness, expand HIV testing to groups at higher risk, retain HIV-infected patients in care, reduce HIV transmission rates, and decrease high-risk behaviors that place individuals at risk of HIV acquisition [14].

## 40.5 HIV Virology and the Resulting Host Response

HIV is a retrovirus. As part of their replication cycle, retroviruses reverse-transcribe viral RNA into linear double-stranded DNA, which then incorporates itself into the host genome. It is currently believed that HIV-1 and HIV-2 originated in primates and jumped species to humans in Central and West Africa. Four groups of HIV-1 exist: M (for major), N, O, and P. Group M was the main cause of the global HIV pandemic and consists of nine viral subtypes: A–D, F–H, J, and K. Subtype B is the predominant subtype found in the Americas, Western Europe, and Australia, while subtype C is the primary type found in Africa and India [15]. HIV-2 causes a similar illness to HIV-1, but immunodeficiency progresses more slowly, and it tends to be associated with lower viral loads in most individuals. Infection with HIV-2 is largely confined to West Africa and in countries with strong socioeconomic ties to West Africa such as France, Spain, Portugal, and former Portuguese colonies of Brazil, Angola, Mozambique, and parts of India [1, 16]. A distinguishing feature of HIV-1 infection is the progressive depletion of CD4+ T cells, the primary target cell for HIV. Infection and depletion of CD4+ T cells account for many of the manifestations of HIV [17].

HIV enters CD4+ T-lymphocytes via the CD4 receptor and a chemokine co-receptor, either CCR5 or CXCR4, as a dual-receptor system. The virus initiates infection by via the viral glycoprotein, gp 120, which binds to the CD4 receptor found on CD4+ T-lymphocytes and subsets of other mononuclear cells [3] (Fig. 40.2). The HIV envelope fuses with the target, allowing release of the viral core into the host cell. Next, viral DNA is produced through the action of virus-encoded reverse transcriptase on the viral RNA genome. HIV

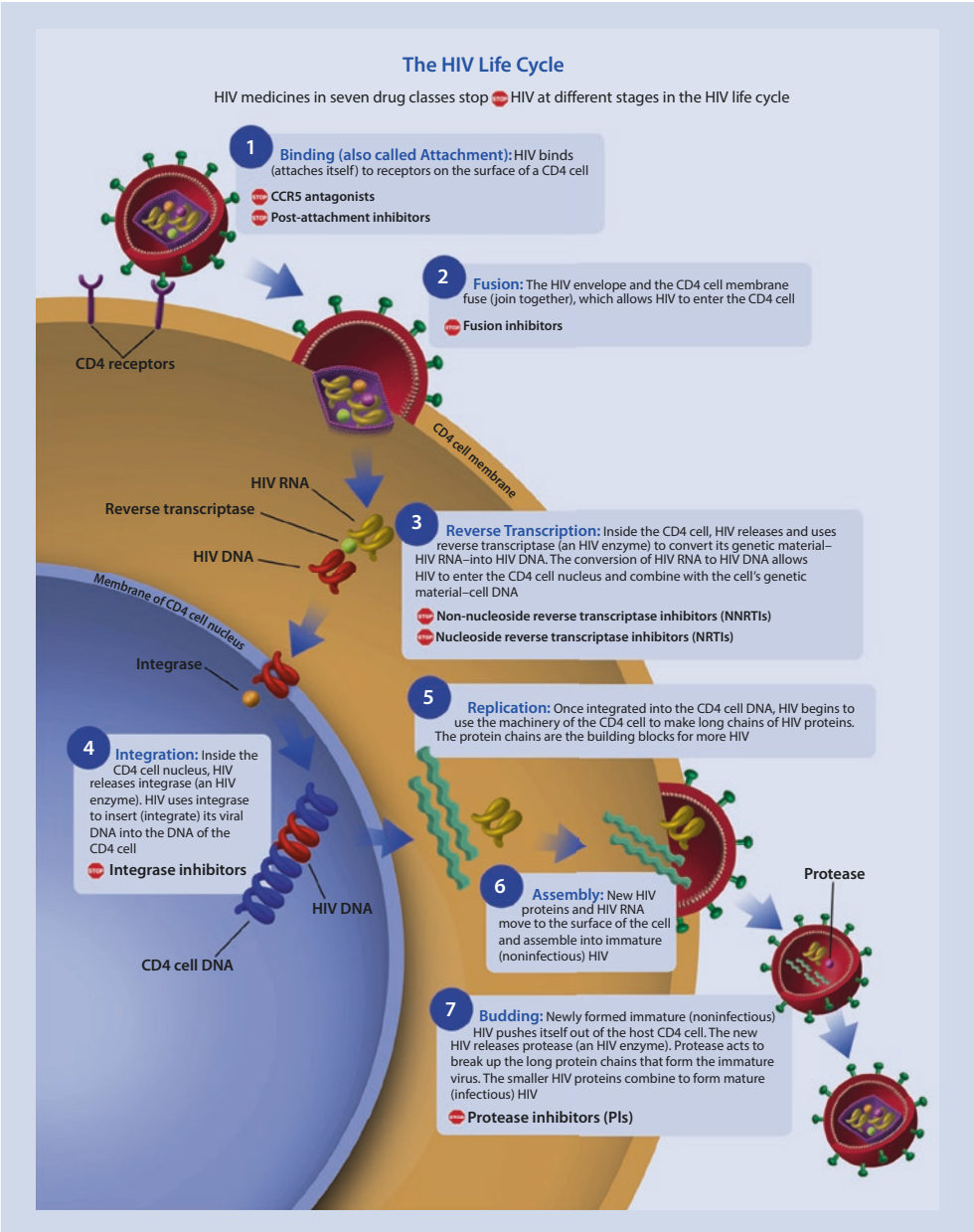


**Fig. 40.2** Schematic of the HIV life cycle and associated targets of antiretroviral therapy. (Reproduced from AIDSinfo, The HIV Life Cycle) [31]

DNA is then transported into the target cell nucleus where it integrates into the host cell DNA genome through the action of virus-encoded integrase. During HIV replication, new viral RNA is used as genomic RNA and as the template for translation of viral proteins. The components assemble and mature into new, infectious virions [18].

It is now known that the cellular and anatomic sites of HIV replication influence the disease progression, the ability of antiretroviral therapy to reduce viremia, and the capacity to establish a viral reservoir. The HIV reservoir is defined as a group of cells that are infected with HIV but that are not actively producing new virions [19].

### 40.5.1 HIV Transmission

Modes of HIV transmission include direct sexual contact with semen, vaginal fluid, or blood that contains the virus, exposure to blood products derived from HIV-infected individuals, vertical transmission from mother to infant, and accidental occupational exposure. Multiple variables influence the probability of HIV transmission, including the dose inoculum of the virus, the route of exposure, the genetic background of the host, and concomitant infections that are often associated with microscopic breaks in the skin or mucous membranes providing the virus with direct access to the bloodstream [20].

Once infected with HIV, viremia allows for widespread dissemination to target cells of the lymphoid tissue and the central nervous system. During early HIV infection, as the HIV virus infects CD4+ T cells, detectable blood viral RNA levels are quite high, while the CD4+ T-cell lymphocyte count drops only transiently, if at all [21]. Hepatic transaminitis, mild anemia, and thrombocytopenia are also commonly seen during acute HIV infection [22]. HIV has marked genetic diversity because reverse transcriptase does not have proofreading activity like DNA polymerases do. The lack of proofreading during reverse transcription results in a high mutation rate broad genetic variation [1]. HIV also has the capacity to integrate its genome into that of the target cell, so despite treatment with highly effective antiretroviral therapy, the virus maintains a latent reservoir of infected cells [19].

## 40.6 Basic Concepts

### 40.6.1 Human Immunodeficiency Virus Replication

HIV is a lentivirus, which is a type of retrovirus. These viruses are enveloped single positive-strand RNA viruses that replicate through a DNA intermediary. There are two types of HIV, HIV-1 and HIV-2. HIV-1 is the most common type worldwide, while HIV-2 is most common in western Africa. The genome for HIV contains ~9000 base pairs that encode 9 genes that produce 15 proteins [23].

HIV is acquired across mucosal surfaces or via direct injection. The cell surface protein gp120 binds to CD4, a marker most commonly found on CD4 T-helper lymphocytes and macrophages. With interactions from the heptahelical transmembrane chemokine receptors CXCR4 and CCR5, the viral transmembrane protein gp41 inserts itself into the T-cell membrane, causing the virus and the cell to fuse. A protein capsid then enters the host cell releasing two viral strands of RNA and three enzymes: reverse transcriptase, integrase, and protease. Reverse transcriptase takes the single-strand RNA and creates an RNA-DNA hybrid. Once the hybrid is complete, the RNase H domain of reverse transcriptase removes the RNA strand prior to reverse transcriptase forming the complimentary strand to the now single-stranded viral DNA. Once a double-stranded DNA copy of the viral RNA is formed, integrase cleaves two nucleotides from each 3-prime end, forming sticky ends. Integrase then transports the DNA into the cell's nucleus and inserts the DNA into the host genome. When the cell becomes activated, host RNA transcriptase copies the viral DNA forming mRNA templates that are cleaved by viral protease, which forms the viral enzymes and cell surface markers needed to generate new viral particles. Once RNA templates of the virus and the necessary proteins are assembled, new viral particles are able to bud off from the infected host cell and migrate to infect other CD4 T-helper cells [24, 25]. ARV medications target key steps in the viral life cycle.

## 40.7 Risk Factors for the Transmission of HIV

The rate of transmission of HIV is affected by the viral load present in the body fluid that the individual has been exposed to and by the specific nature of exposure. Direct infusion of an HIV-contaminated blood product is associated with more than a 90% risk of transmission (Table 40.1). In the United States, donated blood has been screened since in the late 1980s. Use of screen-negative blood and blood products is associated with an estimated risk of less than one case of transfusion-associated HIV per 1.5 million transfusions. Only one possible case has been identified since 2002 [26]. Receptive anal intercourse, the form of intercourse carrying the highest risk, has a 1.6% risk of transmission per exposure. Needle sharing among HIV-discordant intravenous drug users carries a risk of approximately 0.7% per exposure [27]. HIV transmission risk estimates discussed here and shown in Table 40.1 do not account for variations in the viral load at the time of the exposure. Data are now clear that individuals who have a sustained undetectable viral load are highly unlikely to transmit HIV to a susceptible sexual contact no matter what the nature of the exposure is [28].

One of the earliest and greatest achievements in reducing HIV transmission was the reduction of perinatal

**Table 40.1** Risk of HIV transmission by type of exposure [27]

| Type of exposure | Risk per 10,000 exposures | Percent risk |
|---|---|---|
| **Parenteral** | | |
| Blood transfusion | 9250 | 92.5 |
| Needle sharing | 63 | 0.63 |
| Needle stick | 23 | 0.23 |
| **Sexual** | | |
| Receptive anal intercourse | 138 | 1.38 |
| Insertive anal intercourse | 11 | 0.11 |
| Receptive penile-vaginal intercourse | 8 | 0.08 |
| Insertive penile-vaginal intercourse | 4 | 0.04 |
| Receptive oral intercourse | Low | |
| Insertive oral intercourse | Low | |
| **Miscellaneous** | | |
| Biting | Negligible | |
| Spitting | Negligible | |
| Skin exposure to body fluids | Negligible | |
| Sharing sexual toys | Negligible | |

acquisition of HIV. Prior to the availability of antiretroviral medications, perinatal transmission of HIV infection from an infected mother to her infant carried a risk of approximately 20%. In 1994, the Pediatric AIDS Clinical Trials Group released the results of protocol 076 which documented a 66% reduction in the rate of transmission of maternal-to-infant HIV when intrapartum zidovudine was administered to the mother during labor and then subsequently administered to the newborn during the first 6 weeks of life [29]. In children born to women with known HIV, the ARV regimen used in the infants is based upon risk factors including duration of rupture of membranes, maternal viral load, the use of fetal scalp electrodes, maternal viral resistance pattern, and compliance with HIV medications prior to delivery. Once delivered, low-risk children are treated with AZT for 4–6 weeks, while those deemed to be at higher risk are treated with AZT for 6 weeks while also receiving other active agents such as nevirapine (NVP) and lamivudine (3TC). For patients whose mothers have an undetectable viral load at the time of delivery and who are treated with AZT after birth, there is a less than 1% risk of acquiring HIV [30].

**Exercises are included at the end of** ► Chap. 41**.**

## 40.8 Summary

HIV remains a disease that can easily mimic the signs and symptoms of other illnesses, and coupled with the stigma of diagnosis, the disease is often not tested for as frequently as it should. However, a careful review of a patient's history, and a thorough examination, will often provide clues that HIV should be expected. Moreover, it should become common practice to test all sexually active individuals during their annual wellness checks. Should HIV be suspected, there are now tests that are both highly sensitive and specific for the diagnosis. And while HIV does not have a cure, advances in therapeutics since HIV/AIDS was first described in the early 1980s have significantly reduced the morbidity and mortality associated with the disease so that it is now thought of more as a common chronic medical condition as opposed to the uniformly lethal diagnosis of the 1980s and early 1990s.



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# Human Immunodeficiency Virus II: Clinical Presentation, Opportunistic Infections, Treatment, and Prevention

**Fever, Pharyngitis, and Lymphadenopathy with Prolonged Fatigue Weight Loss with Recurrent Infections**

*Ami Multani, Bradford Becken III, and Simi Padival*




J. Domachowske (ed.), *Introduction to Clinical Infectious Diseases*,
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**Learning Objectives**

- Understand the clinical presentation of acute HIV infection
- Recognize the appropriate laboratory tests used for the diagnosis of HIV infection
- List the classes of and uses for antiretroviral medications
- Describe AIDS defining conditions, including opportunistic infections
- Discuss effective strategies used to prevent HIV infection

» "There is no story in global health as transformative, awe-inspiring, and yet as tragic as the AIDS pandemic. The disease was unknown only a generation ago – a medical curiosity among young gay men in New York and San Francisco in June 1981. Within a few short years, AIDS could be found on every continent, enveloping the world to become one of the most devastating pandemics in human history. It has caused untold human suffering, social disintegration and economic destruction." – Lawrence O. Gostin [1]

## 41.1 Introduction

Since it was first described in the medical literature in 1981, the battle led by scientists, physicians, advocacy groups, educators, activists, and policy makers has resulted in dramatic advances in the diagnosis and management of HIV/AIDS that are changing this disease from a "death sentence" to a more manageable chronic disease [2–4].

Diagnosing HIV infection requires a high index of suspicion, recognition of the clinical manifestations, as well as knowledge of the diagnostic tools required in order to make an accurate and timely diagnosis [5]. Infection with HIV/AIDS can be a shocking and isolating diagnosis for an individual to receive. Today, access to care, early diagnosis, regular monitoring of the disease, treatment with highly active antiretroviral therapy (HAART), and prophylaxis and treatment of opportunistic infections have increased survival rates and changed the natural history of HIV infection wherever these resources are made generally available [6].

## 41.2 HIV Disease Progression

### 41.2.1 Acute HIV Infection

Individuals acutely infected with HIV can present with a constellation of symptoms ranging from an influenza-like illness with a maculopapular rash to a nonspecific chronic illness with fatigue and wasting [6]. The symptoms experienced during acute symptomatic HIV infection are referred to as the acute retroviral syndrome [7]. Individuals with acute HIV infection commonly complain of fever, fatigue, myalgia, skin rash, and headache, with or without pharyngitis, cervical adenopathy, arthralgia, night sweats, or diarrhea [5]. Clinically, the constellation of fever, fatigue, myalgia, rash, pharyngitis, and cervical adenopathy is quite typical for acute mononucleosis secondary to infection with Epstein-Barr virus or cytomegalovirus. Individuals with a mononucleosis-like syndrome should be tested for acute HIV infection unless the etiology of their illness has already been otherwise established. It is important to note that up to 60% of individuals with acute HIV infection do not recall experiencing a recent medical illness suggesting that many episodes of acute retroviral syndrome are minimally symptomatic [23, 24].

### 41.2.2 Early HIV Infection

Early HIV infection generally refers to the first 6 months of the infection. During this time many patients experience transient or vague symptoms. Some are asymptomatic. Initially, there is a robust and rapid period of viral replication with infection of CD4+ T-cells. Blood viral RNA levels are generally very high (>100,000 copies/mL) and can be associated with a transient drop in the CD4+ T-cell count. During the ensuing 3–6 months, the HIV viral load (quantitative HIV RNA level) will drop 3–5 logs, in association with CD4+ T-cell recovery [8]. HIV RNA levels may reach a steady state, or set point, by 3–6 months after the primary HIV infection. HIV RNA levels may be variable, but, overall, the viral load is directly associated with the rate of disease progression [8, 9]. CD4+ T-cell counts recover during the first month after infection as CD8+ T-lymphocytes help to control viral replication [10]. Without treatment, the decline in CD4+ T-cell counts occurs over time, occurring more rapidly in those patients with prolonged symptoms at the time of primary infection [8]. Though there may be clinical latency during this period, there is great replicative activity within lymphoid tissue, which acts as a major reservoir for the virus [11]. As HIV infection progresses, there is a gradual loss of this partially effective immune response. Even the once-limited control over virus replication is lost, leading to more active viral replication and further impaired cellular immune function.

### 41.2.3 Chronic HIV Infection

Chronic HIV infection occurs after the set point has been reached during early infection but before the occurrence of severe immunosuppression, defined as a peripheral CD4+ T-lymphocyte count of fewer than 200 cells/mm$^3$. During this time, HIV RNA levels are typically stable as the patient experiences a gradual but progressive decline in circulating CD4+ T-cell numbers. This decline is most rapid during the first year of infection, after which the drop slows to a rate of about 50 cells/mm$^3$ per year [12]. The rate of CD4+ T-cell loss is highly variable from patient to patient, but on average the threshold of fewer than 200 cells/mm$^3$ is reached over an 8- to 10-year period. [13–15].

While patients are generally asymptomatic during this period, clinical manifestations may include generalized lymphadenopathy, peripheral neuropathy, or illnesses heralding the decline in effective immune function including recurrent or persistent oral or vulvovaginal candidiasis, reactivation of varicella zoster virus causing shingles, immune-mediated thrombocytopenic purpura, or oral hairy leukoplakia [16].

### 41.2.4 Advanced HIV and AIDS

Uncontrolled HIV eventually causes sufficient loss of CD4+ T-cells leading to significant immunosuppression. From the laboratory perspective, acquired immunodeficiency syndrome (AIDS) is defined by a CD4+ T-cell count of 200 or fewer cells/mm$^3$. While this threshold is commonly used to categorize the HIV patient as having AIDS, there are other illnesses that are also considered AIDS defining. These illnesses typically occur when the CD4+ T-cell count falls below 200 cells/mm$^3$ for a sustained period of time; however, they can also occur at higher cell counts [16, 17]. Prior to the era of antiretroviral therapy (ART), AIDS-defining illnesses accounted for most of the morbidity and mortality associated with HIV infection. AIDS-defining illnesses include opportunistic infections, certain malignancies, and syndromes associated with HIV infection that may not be otherwise clearly defined. A complete list of AIDS-defining conditions is presented in Table 41.1. In the USA, the most common AIDS-defining illnesses seen in HIV patients during the 1990s included *Pneumocystis jirovecii* pneumonia, esophageal candidiasis, Kaposi sarcoma, wasting syndrome, and disseminated *Mycobacterium avium* infection [18]. Once the CD4+ T-cell count falls below 200 cells/mm$^3$, the median time to developing an AIDS-defining condition is 12–18 months without ART [19]. Patients who progress to advanced HIV infection, commonly defined as a CD4+ T-cell count of less than 50 cells/mm$^3$, have a median survival of 12–18 months [20, 21].

**Table 41.1** AIDS-defining conditions in HIV-infected individuals [57]

| | |
|---|---|
| Bacterial infections, multiple or recurrent[a] | Disseminated or extrapulmonary infection with *Mycobacterium avium* complex or *Mycobacterium kansasii* |
| Candidiasis of the bronchi, trachea, or lungs | Kaposi sarcoma |
| Candidiasis of the esophagus | Lymphoma, Burkitt (or equivalent term) |
| Cervical cancer, invasive[b] | Lymphoma, immunoblastic (or equivalent term) |
| Coccidioidomycosis, disseminated or extrapulmonary | Lymphoma, primary, of the brain |
| Cryptococcosis, extrapulmonary | *Mycobacterium tuberculosis* of any site, pulmonary, disseminated, or extrapulmonary[b] |
| Cryptosporidiosis, chronic intestinal (>1 month's duration) | *Mycobacterium*, other species or unidentified species, disseminated or extrapulmonary |
| Cytomegalovirus disease (other than the liver, spleen, or nodes), onset at age >1 month | *Pneumocystis jirovecii* pneumonia |
| Cytomegalovirus retinitis (with loss of vision) | Pneumonia, recurrent[b] |
| Encephalopathy attributed to HIV[c] | Progressive multifocal leukoencephalopathy |
| Herpes simplex virus infection causing chronic ulcers (>1 month's duration) or bronchitis, pneumonitis, or esophagitis (onset at age > 1 month) | *Salmonella* septicemia, recurrent |
| Histoplasmosis, disseminated or extrapulmonary | Toxoplasmosis of the brain, onset at age > 1 month |
| Isosporiasis, chronic intestinal (>1 month's duration) | Wasting syndrome attributed to HIV[c] |

[a]Only among children aged <6 years
[b]Only among children aged ≥6 years, adolescents, and adults
[c]Suggested diagnostic criteria for these illnesses, which might be particularly important for HIV encephalopathy and HIV wasting syndrome, are described in MMWR Recomm Rep 1994; 43 (No.12) and MMWR Recomm Rep 1992; 41 (No.17)

### 41.2.5 HIV Controllers

A small percentage of HIV-infected individuals not on ART do not develop significant progression of disease. These individuals tend to remain asymptomatic with stable CD4+ T-cell counts and low levels of HIV viremia. Long-term non-progressors are individuals without significant disease progression for many years while maintaining a minimal CD4+ T-cell count of 500 cells/mm$^3$, likely as a result of sustained immune control limiting their HIV viremia to fewer than 10,000 copies/mL [22, 23]. An even smaller percentage of individuals are considered elite controllers. Elite controllers have no detectable viremia and preserved CD4+ T-cell counts for a prolonged period of time without any disease progression [23]. Despite the ability to control HIV viremia without ART, these individuals may still be at risk of other complications of chronic HIV infection including noninfectious complications such as cardiovascular disease [24]. While viral loads are low in non-progressors and absent in elite controllers, significant immune activation does occur. These individuals, therefore, still benefit from ART [11].

## 41.3 Clinical Evaluation of the HIV-Infected Individual

### 41.3.1 Physical Examination

Initial evaluation of the HIV-infected patient includes a comprehensive medical history, including a thorough social, travel, and medication history, and a complete physical examination. During the physical examination, the provider should be sure to complete an assessment for palpable lymphadenopathy as nonspecific, small, mobile nodes are frequently seen in HIV-infected patients [6]. Examination of the head, eyes, ears, nose, and throat should note any presence of pharyngeal edema or hyperemia or mucocutaneous ulcerations [7, 25]. One should also evaluate for oropharyngeal candidiasis (thrush), angular cheilitis, stomatitis, and oral hairy leukoplakia, a manifestation of infection with Epstein-Bar virus in immunosuppressed individuals. A complete eye examination should be performed at baseline. If the patient's CD4+ T-cell count is below 50 cell/mm$^3$, and there are changes in vision, a detailed ophthalmologic examination is important to evaluate for the possible presence of cytomegalovirus (CMV) retinitis or ocular syphilis. The cardiopulmonary examination should focus on any symptoms of shortness of breath, cough, or hemoptysis to help assess for pneumonia, pneumothorax (which can be related to *P. jirovecii* pneumonia), pericarditis, or cardiomyopathy [6]. The gastrointestinal examination should start by assessing for the presence of nausea, dysphagia, or anorexia. Right upper quadrant abdominal pain should raise concern for cholelithiasis or hepatitis, while left upper quadrant pain is more concerning for pancreatitis or disease associated with the stomach or spleen. Diarrheal illness is common in HIV infection and can be caused by a wide variety of pathogens including bacteria (e.g., *Salmonella* species, *Shigella* species), viruses (e.g., CMV), or parasites (e.g., *Cryptosporidium parvum*). The presence of rectal pain should be evaluated for signs of trauma, abscess, proctitis, fissures, or masses [6]. The genitourinary examination should evaluate for findings that may consistent with the presence of other sexually transmitted diseases, all of which can be more difficult to diagnose and treat in the setting of HIV infection. HIV-infected women should undergo a full pelvic examination with regular Pap smear screening because of their increased incidence of cervical dysplasia and more rapid progression to cervical cancer [6]. Neurologic signs and symptoms associated with HIV infection and its complications are highly variable. Acute complaints of headache or visual loss may be an evaluation for meningitis, encephalitis, cerebral toxoplasmosis, progressive multifocal leukoencephalopathy, retinitis, or CNS lymphoma. Memory loss with poor concentration may be a sign of HIV-associated dementia. The dermatologic examination should focus on any type of rash or change in skin pigmentation, including careful visual inspections of the palms, soles, and anogenital area [6].

### 41.3.2 Laboratory Evaluation

The initial symptoms of HIV infection can be nonspecific and difficult to distinguish from other viral illnesses unless appropriate laboratory testing is performed [5]. A diagnosis of HIV should be made from two separate blood samples with the tests performed varying based on a patient's age. As antibodies to the HIV virus cross the placenta and may persist in the blood of the child born to an infected mother for up to 15 months, antibody-derived tests are of no utility in the diagnosis of exposed newborns. Instead, in an exposed newborn, qualitative RNA PCR is the test of choice. DNA PCR has been well studied and is reliable; however, commercially available and FDA-approved DNA PCR tests are not available. Beyond the newborn period, fourth-generation antibody and antigen tests are preferred; however, for very early acute infections, viral load testing (quantitative HIV RNA PCR) may be necessary. Fourth-generation combination antigen and antibody immunoassay, **and** a quantitative RNA polymerase chain reaction-based assay to determine the HIV viral load [26, 27]. Current fourth-generation HIV-1 antibody tests and p24 antigen tests typically become positive approximately 15–20 days after HIV exposure. A detectable HIV RNA viral load is present within 5–15 days post-HIV exposure [28].

Perinatal transmission of HIV infection from an infected mother to her infant is preventable with proper intrapartum and postpartum management. Women who have not had HIV testing during the current pregnancy who present in labor should have a rapid HIV test performed so that results are available as soon as possible. Rapid HIV tests are preferred in this setting because they allow the initiation of ARV therapy in the expectant mother, if she has not yet delivered, and the initiation of ARV therapy in the newborn as soon after birth as possible. This strategy dramatically reduces the risk of perinatally transmission of HIV from the mother to her child.

When a patient is newly diagnosed with HIV infection, additional laboratory testing is necessary to establish baseline laboratory values, to document the current degree of immunosuppression, to estimate the likelihood and rate of HIV disease progression, and to guide decisions regarding optimal and appropriate ART. During subsequent clinical evaluations, laboratory testing is used to monitor the virologic response to ART, to monitor for potential toxicities of medications, and to continue to screen for common and/or preventable associated illnesses [6] (Table 41.2).

## 41.4 Treatment

### 41.4.1 Basics of ART: Antiretroviral Therapy

The first antiretroviral medication, zidovudine (ZDV), was introduced in 1996. Since that time, dozens of highly effective medications have become available for use in combination

**Table 41.2** Diagnostic laboratory testing used for the diagnosis and monitoring of HIV infection

| Laboratory test | Rationale | Suggested monitoring interval |
|---|---|---|
| CD4+ T-cell count<br>May include additional lymphocyte immunophenotyping, often referred to as "lymphocyte subsets" | Evaluation of degree of immunosuppression<br>Guiding initiation of prophylaxis for opportunistic infections<br>Prognostic information<br>Monitoring of efficacy of therapy | Baseline, then every 3–6 months if not on ART, every 3–6 months for the first 2 years of ART and for patients who struggle with adherence<br>Every 12 months after 2 years of ART with sustained, suppressed viral load |
| Quantitative HIV RNA PCR, commonly referred to as an HIV viral load test | Monitoring of HIV replication activity<br>Evaluating the efficacy of the current ART regimen | Baseline, then at time of ART initiation or modification<br>Repeat 2–8 weeks after ART initiation or modification<br>Every 3–6 months for the first 2 years of ART, then every 6 mos if stable |
| HIV genotyping<br>Commonly referred to as HIV resistance testing | Evaluation for mutations associated with resistance to ART medications<br>To guide changes in treatment regimens | Baseline<br>At time of ART initiation<br>If patient has virologic failure |
| CBC with differential | Monitoring for hematologic drug toxicities | Baseline<br>At time of ART initiation or modification<br>Every 6 months<br>Every 3–6 months if not on ART or as clinically indicated |
| Serum electrolytes, creatinine, and hepatic transaminases | Evaluation of baseline renal and liver function<br>Monitoring for drug toxicities | Baseline<br>At 2–8 weeks after ART initiation or modification<br>Every 3–6 months<br>More frequently in patients as clinically indicated<br>Every 6–12 months if not on ART |
| Fasting lipid profile | Monitoring for drug toxicities | Baseline<br>At time of ART initiation or modification<br>Every 6 months if abnormal<br>Every 12 months if benign |
| HLA-B*5701 | Assess genetic risk of hypersensitivity reaction to abacavir | Prior to initiation of abacavir as part of an ART regimen |
| G6PD activity | Screening for G6PD deficiency prior to starting therapy with an oxidant drug | Baseline |
| Tropism testing | When considering the use of a CCR5 antagonist as part of an ART regimen | Prior to initiation of a CCR5 antagonist |
| Urinalysis and creatinine clearance | Evaluation for the risk of nephropathy and prior to using potentially nephrotoxic medications | Baseline<br>Prior to initiation or modification of ART<br>Every 6 months if tenofovir is included in the ART regimen, otherwise every 12 months |
| Acute hepatitis profile | Diagnosis of viral hepatitis<br>Evaluation for prior vaccination and immunity to hepatitis A and hepatitis B | Baseline<br>During potential acute infection |
| Rapid plasma reagin | Screening for syphilis<br>Monitoring of response to syphilis therapy | Baseline<br>Annually<br>During new symptoms |
| Anti-toxoplasma antibody (IgG) | Screening for prior exposure to *Toxoplasma gondii*<br>Guide future diagnostic and empiric management | Baseline<br>Annually in patients who are IgG negative |
| Tuberculosis screening<br>May be done using tuberculin skin testing or interferon gamma release assay | Screening for active or latent tuberculosis | Baseline<br>Annually if possible exposures |

ART regimens. The availability of ART has been associated with a tremendous decline in the morbidity and mortality associated with HIV in all areas of the world where it has been made available. In one study, mortality declined from 29.4 per 100 person-years in 1995 to 8.8 per 100 person-years in 1997, just from the introduction of ZDV [29]. Reductions in mortality were noted regardless of factors such as age, sex, race, or mode of HIV transmission [29].

Historically, guidance and opinion on when to start a patient on antiretroviral therapy have varied. Individuals with CD4+ T-cell counts less than 350 cells/mm$^3$ who are treated with ART have reduced morbidity, slower progression to AIDS, and lower mortality from opportunistic infections [30–32]. In contrast, ART was once delayed in those with preserved CD4+ T-cell counts given the potential toxicities associated with treatment and lack of known benefit for patients with higher CD4+ T-cell counts. More recent data clearly supports the use of ART regardless of CD4+ T-cell counts [33–36]. Many of the newer antiretroviral medications are much better tolerated and are associated with fewer toxicities than their predecessors. Thus, the current goals of treatment for HIV infection are to prevent or reduce HIV-associated complications by suppressing any HIV viremia, thereby preserving immune function and preventing progression to AIDS. Suppression of HIV viremia also significantly reduces the risk of transmission to HIV seronegative sexual partners by as much as 96% [37, 38].

Some individuals are at particularly high risk for HIV-associated morbidity and mortality warranting urgent evaluation and initiation of treatment. Conditions of elevated risk include pregnancy, coinfection with hepatitis B virus, and patients who have already developed complications from HIV. Individuals with acute HIV infection (acute retroviral syndrome) should also be considered for immediate therapy to reduce their potential for transmission to others during their period of highest viremia.

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### 41.4.2 Antiretroviral Therapy Options

Currently six classes of medications are available for the treatment of HIV infection (Table 41.3). Combination therapy is warranted to reduce the emergence of drug resistance.

Nucleoside reverse transcriptase inhibitors (NRTIs) are nucleoside analogs, and once they are phosphorylated by the host cell, they compete with other nucleosides for inclusion into DNA copies being created by reverse transcriptase. Once NRTIs are included into a growing DNA chain, transcription is terminated. Nucleotide reverse transcriptase inhibitors (NrTRIs) are similar to NRTIs except that they do not require phosphorylation by host kinases. Tenofovir disoproxil fumarate (TDF) was first approved in 2001, and a revised formulation, tenofovir alafenamide (TAF), was approved in 2016.

Unlike NRTI, non-nucleoside reverse transcriptase inhibitors (NNRTIs) bind to reverse transcriptase, inactivating it.

**Table 41.3** The six classes of available antiretroviral medications

| | Class | Examples |
|---|---|---|
| 1 | Nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs) | Zidovudine (ZDV), lamivudine (3TC), emtricitabine (FTC), abacavir (ABC), tenofovir disoproxil fumarate (TDF), tenofovir alafenamide (TAF) |
| 2 | Non-nucleoside reverse transcriptase inhibitors (NNRTIs) | Efavirenz (EFV), rilpivirine (RPV), nevirapine (NVP), etravirine (ETR) |
| 3 | Protease inhibitors (PIs) | Atazanavir (ATV), darunavir (DRV) |
| 4 | Integrase strand transfer inhibitors (INSTIs) | Raltegravir (RAL), elvitegravir (EVG), dolutegravir (DTG) |
| 5 | Fusion inhibitor (FI)[a] | Enfuvirtide (T-20) |
| 6 | CCR5 receptor antagonist[a] | Maraviroc |

[a]Typically used in salvage regimens for treatment-experienced individuals with HIV infection

Common FDA-approved NNRTIs are nevirapine (NVP) 1996, efavirenz (EFV) 1998, etravirine (ETR) 2008, and rilpivirine (RPV) 2011. NNRTIs are not used as monotherapy and are always combined with medications from other classes owing to the rapid development of resistance if used as monotherapy.

Protease inhibitors (PIs) bind to and prevent the action of HIV protease, which is needed to cleave viral proteins into their appropriate shape and length. PIs were the first class other than NRTIs and NNRTIs to be developed.

Integrase Inhibitors: first approved by the FDA in 2007, integrase inhibitors (II) prevent insertion of viral DNA into the host genome. Commonly used integrase inhibitors include raltegravir approved for use in 2007, dolutegravir approved in 2013, and elvitegravir approved in 2014. Integrase inhibitors are included in several of the most recent multi-medication combination tablets including Genvoya ® (elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide) approved in 2015 and Juluca (dolutegravir and rilpivirine) approved in 2017.

Fusion and entry inhibitors aim to stop the earliest stages of the viral replication cycle. Maraviroc first became available in 2007. This drug prevents the HIV transmembrane protein gp120 from associating with CCR5, a co-receptor with CD4, on the surface of T-helper lymphocytes and macrophages. By blocking gp120's interaction with CCR5, the entry of the viral protein capsid into the host cell is prevented. Enfuvirtide (T-20), FDA approved in 2005, is a fusion inhibitor that binds to the viral protein gp41. After the interaction between gp120 and CD4 and either CCR5 or CXCR4, gp41 undergoes a conformational change and inserts itself into the host membrane, allowing fusion. By binding to gp41, T-20 prevents this step.

**Table 41.4** Opportunistic infection prophylaxis based on CD4+ T-cell counts [58]

| CD4+ T-cell count | Opportunistic infection | Recommended prophylaxis |
|---|---|---|
| All patients | Tuberculosis (TB) | Latent TB therapy if warranted based on testing |
| ≤250 cells/mm$^3$ | Coccidioidomycosis | Fluconazole in patients who live in endemic regions and have positive serology |
| ≤200 cells/mm$^3$ | *Pneumocystis jirovecii* | Trimethoprim-sulfamethoxazole discontinue once CD4 > 200 cells/mm$^3$ for more than 3 months |
| ≤100 cells/mm$^3$ | Toxoplasmosis | Trimethoprim-sulfamethoxazole in patients with positive serology discontinue once CD4 > 200 cells/mm$^3$ for more than 3 months |
| ≤50 cells/mm$^3$ | *Mycobacterium avium* complex (MAC) | Azithromycin; discontinue when CD4 > 100 cells/mm$^3$ for more than 3 months |

In patients who are treatment naïve, the initial ARV regimen mainly consists of two NRTIs, as the backbone of therapy, plus a third drug from another class of medication, such as an NNRTI, PI, or INSTI. Medication formulations now exist that include two, three, or four medications in a single pill in an effort to reduce the burden of taking multiple pills at one time. Several of the available medications now have serum half-lives that permit once-daily dosing. Available treatment regimens now include several "one pill, once a day" options to deliver the necessary combination therapy. Current guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents from the US Department of Health and Human Services include options such as tenofovir alafenamide with emtricitabine, plus either dolutegravir or raltegravir; tenofovir alafenamide with emtricitabine, elvitegravir, and cobicistat; or abacavir with emtricitabine and dolutegravir (in patients who are negative for HLA-B*5701) as preferred regimens [11, 39, 40].

Other factors should also be taken into consideration when choosing a regimen, including patient preference regarding pill burden, dosing frequency, comorbid conditions such as cardiovascular or renal disease, drug interactions, side effect profile, and known potential toxicities. Treatment-experienced patients who have failed prior regimens should undergo HIV genotype testing to assess for resistance mutations that may impact HIV suppression before choosing a new treatment regimen [41].

### 41.4.3 Other Treatments for HIV Infection

Patients with HIV infection may also benefit from treatment with other medications depending on the clinical circumstances. Patients with low CD4+ T-cell counts, for example, may need to take antibiotics to help prevent specific opportunistic infections (OIs) such as *Pneumocystis jirovecii* pneumonia [16, 18]. Table 41.4 outlines the common OI prophylaxis recommendations based on the patient's CD4+ T-cell count.

Treatment innovations for the pediatric population, even in the developed world, have lagged behind. Not all medications are available as a child-friendly preparation (liquid or sprinkles), and some liquid medications are very unpalatable. Owing to the need for weight-based dosing, most single-pill combinations are not available to pediatric patients. However, in 2017, single-pill combinations had started to be investigated in patients weighing at least 25 kilograms.

## 41.5 Complications Associated with HIV Infection

### 41.5.1 Immune Reconstitution Inflammatory Syndrome

While ART has dramatically reduced morbidity and mortality in HIV-infected individuals, complications associated with the initiation of ART have been noted. Immune reconstitution inflammatory syndrome (IRIS) is a paradoxical worsening of preexisting infections or noninfectious conditions that were previously controlled or treated or an unmasking of subclinical or unknown infections or noninfectious conditions [42, 43]. IRIS occurs as a result of improved immunologic function as the individual's CD4+ T-cells repopulate during the treatment of their HIV infection. Although the exact mechanisms of action are unclear, it is felt that there is a restoration of pathogen-specific immune responses [44, 45]. It is estimated that as many as 30% of HIV-infected individuals will experience IRIS. Symptoms typically occur between 30 and 40 days after starting ART [45, 46]. Risk factors for IRIS include younger age at time ART initiation, lower CD4+ T-cell count at the time ART is initiated, and high viral load [46]. Typically, the inflammatory response associated with IRIS occurs at the site of the pre-existing infection and is generally self-limited. More severe, even life-threatening IRIS occurs rarely. Common opportunistic infections that are associated with the development of IRIS and general management considerations are summarized in Table 41.5 [42, 46, 47]. Generally speaking, ART should be started early and within 2 weeks of starting treatment for an existing opportunistic infection [11, 38]. ART should be maintained through the clinical course, unless life-threatening symptoms occur requiring that ART be temporarily held

**Table 41.5** Infections associated with the development of IRIS following treatment for HIV infection [42, 45, 46, 47]

| Infection | Clinical manifestation of IRIS | Management |
|---|---|---|
| *Cryptococcus neoformans* | Meningoencephalitis<br>Pneumonia | Antifungal therapy<br>Consider corticosteroids for severe disease<br>Consider delaying ART by 2–10 weeks |
| Cytomegalovirus | Uveitis<br>Retinitis | CMV antiviral therapy<br>Consider corticosteroids (topical, intraocular, or systemic)<br>Continue ART |
| *Mycobacterium tuberculosis* | Pneumonia<br>Lymphadenitis<br>Meningitis<br>Central nervous system (CNS) tuberculoma | Treatment for tuberculosis<br>Consider delaying ART by 8–12 weeks or continue ART if already initiated<br>For severe disease or CNS involvement, use corticosteroids |
| *Mycobacterium avium* complex | Pneumonia | Continue ART |
| JC virus | Progressive multifocal leukoencephalopathy | Continue ART<br>Consider corticosteroids |
| *Pneumocystis jirovecii* | Pneumonia | Continue ART<br>PJP treatment |
| Herpes zoster virus | Worsening vesicular/ulcerative rash | Antiviral therapy<br>Continue ART |
| Hepatitis B virus | Hepatitis | Continue ART<br>Consider a TDF- or TAF-based regimen |
| HHV-8 (associated with Kaposi sarcoma) | Rapid lesion progression, fevers | Continue ART |

and adjunctive therapies with anti-inflammatory medications such as corticosteroids or nonsteroidal anti-inflammatory medications be utilized [11].

#### 41.5.1.1 Opportunistic Infections in AIDS

*Pneumocystis carinii* (now *jirovecii*) (PJP) pneumonia, an unusual fungal infection, was described in all five patients reported in the first case series of what was eventually called AIDS [48A]. Prior to the HIV era, this infection was only seen in severely malnourished infants and among individuals with profound deficiencies in cellular immunity. Among HIV-infected patients, PJP occurs when the CD4+ T-lymphocyte count falls below 200 cells/mm$^3$. Patients with PJP present with cough and shortness of breath associated with hypoxemia. The chest radiograph typically shows bilateral chest infiltrates. The diagnosis can be made by performing direct fluorescent antibody staining or pathogen-specific PCR on sputum or bronchoalveolar lavage fluid. Prevention of PJP is most effective with trimethoprim-sulfamethoxazole; pentamidine, inhaled or intravenous monthly, or atovaquone can be used in patients who have a sulfa drug allergy or G6PD deficiency [48B].

The fungus, *Cryptococcus neoformans*, also causes opportunistic infections in HIV-infected patients with low CD4+ T-lymphocyte counts. *C. neoformans* is an encapsulated yeast acquired by inhalation. Once inhaled, the organism disseminates hematogenously with a proclivity to seed the meninges. Mortality in AIDS patients with cryptococcal meningitis exceeds 10% [48C].

*Mycobacterium* species are responsible for the majority of bacterial opportunistic infections in patients with AIDS. *Mycobacterium avium* complex (MAC) is a ubiquitous environmental pathogen that affects both immunocompromised and immunocompetent hosts. Infected immunocompetent hosts typically develop a chronic lymphadenitis, while severely compromised individuals, such as those with AIDS, develop fevers, weight loss, and anemia from disseminated disease. Prophylaxis against MAC is achieved by administering azithromycin daily once the patient's CD4+ T-lymphocyte counts fall below 50 cells/mm$^3$. Patients who are infected with HIV are also at elevated risk for infection with *Mycobacterium tuberculosis* [48D].

Protozoa can also cause infections in severely immunocompromised patients with HIV infection. The three most common opportunistic protozoal infections seen among patients with AIDS include *Toxoplasma gondii*, *Cryptosporidium* species, and *Isospora belli*. *Toxoplasma gondii* causes chorioretinitis or encephalitis, while *Cryptosporidium* species and *Isospora belli* cause chronic diarrhea, malabsorption, and wasting.

Viral infections can also be problematic for patients with AIDS. Viruses in the *Herpesviridae* family are some of the most troublesome. Herpes simplex viruses 1 and 2 cause intermittent outbreaks in some immunocompetent individuals and can become chronic and/or disseminated in patients who lack cellular immune function, such as those with advanced HIV disease. Cytomegalovirus is associated with esophagitis and retinitis, while Epstein-Barr virus is associated with hairy leukoplakia and may play a role in the development of HIV-associated lymphomas. Human herpesvirus-8 (HHV-8) also has oncogenic potential, being most infamous for its role in causing Kaposi sarcoma, the most common malignancy diagnosed in individuals with HIV infection [48E].

Non-oncogenic and oncogenic human papillomavirus (HPV) serotypes can also be particularly aggressive in individuals living with HIV infection. For example, patients with HPV type 6 infection are prone to developing giant

condylomata which can become disfiguring. The vast majority of low-grade anogenital dysplasias affecting immunocompetent adolescents and adults caused by oncogenic HPV types 16 and 18 resolve spontaneously, largely due to the effector functions of an intact cellular immune response. Those who do develop persistent infection typically won't develop malignant changes for more than a decade. In contrast, individuals with HIV infection and AIDS can progress from low- to high-grade dysplasias to carcinoma in situ to cancer within 2 years or even less.

### 41.5.2 Other Complications

HIV infection is also associated with an increased risk of complications that can affect organ systems other than the immune system. Complications may include metabolic and endocrine changes, such as dyslipidemia, lipodystrophy, osteoporosis, and diabetes mellitus; malignancies, including Kaposi sarcoma, cervical cancer, anal cancer, central nervous system lymphoma, cardiovascular disease, and renal disease; and neurologic manifestations such as neuropathy or dementia. Individuals may also be at risk for other sexually transmitted infections. These risks and complications may stem from HIV infection, and the associated cellular immunodeficiency may represent adverse effects from ongoing treatment regimens or may be a direct consequence of ongoing risk behavior. Comprehensive care of HIV-infected individuals demands expertise in screening and managing a wide array of infectious and noninfectious complications [11].

## 41.6 HIV Prevention

Since the start of the AIDS pandemic, a tremendous amount has been learned about HIV transmission and prevention, yet thousands continue to be newly infected every day [48]. The HIV pandemic, like many others, occurs within a complex social environment where social norms can affect disease transmission. Examples include specific sexual practices such as receptive anal intercourse, patterns of sexual partnering involving multiple sexual partners, sex inequality, sexual networks, contraceptive choices, recreational use or abuse of substances that decrease sexual inhibitions, and a tenacious stigma that still seems to restrict access to health care for many high-risk and infected individuals [16, 49]. There are multiple dimensions to consider in HIV prevention. No single intervention has been shown to be highly effective by itself. Multiple intervention strategies are therefore necessary if there is any hope to control the pandemic [49].

The most effective intervention to reduce sexual transmission of HIV is effective antiretroviral therapy for infected individuals. It is also imperative to note the importance of using of barrier methods during sexual activity, such as condoms and dental dams, as they have been shown to decrease HIV transmission and acquisition by up to 90–95% when used consistently [50, 51]. Medical male circumcision is also an effective HIV prevention intervention in resource-poor settings [52]. Pre-exposure prophylaxis (PrEP) is a newer and emerging prevention strategy that can be used for individuals known to have a higher risk for HIV acquisition based on behavioral risk factors. PrEP currently refers to the use of the oral antiretroviral therapy combination, tenofovir plus emtricitabine (TDF-FTC), as a once-daily dose each day. This strategy has been shown to effectively reduce HIV acquisition by greater than 90% [53]. Finally, postexposure prophylaxis (PEP) is a strategy implemented for individuals who have a single, isolated high-risk exposure to HIV. In this strategy, a 28-day course of treatment with three antiretroviral drugs is started within 72 h of the exposure. Patients who present more than once with indications from PEP should be counseled on the availability of PrEP if appropriate to the circumstances [54].

A safe and effective HIV vaccine has remained elusive [48F]. Currently, there are multiple other potential prevention strategies that remain under investigation, including HIV vaccines and the use of vaginal and rectal microbicides that target different stages of the HIV life cycle.

## 41.7 Summary

Initial HIV infection is associated with an acute retroviral syndrome that can easily be mistaken clinically as a bout of infectious mononucleosis. HIV infection, unchecked, leads to a gradual and progressive cellular immunodeficiency. Many patients go undiagnosed until they develop unexplained wasting or an unusual opportunistic infection that is typically seen only in immunocompromised patients. Excellent diagnostic testing tools and highly effective treatment regimens for HIV infection have emerged and evolved since the virus was initially identified as the cause of AIDS in the early 1980s. The progress has allowed for tremendous improvements in the prognosis and quality of life for individuals infected with HIV. The life expectancy of individuals with HIV infection who are treated with ART now mirrors that of the general population [55]. While some populations continue to be at high risk for new acquisition of infection, the overall prevalence of HIV has decreased in all developed and most underdeveloped areas of the world. A cure for HIV remains elusive as challenges exist in targeting reservoirs or cells that remain hidden from host defense and therapeutic interventions. Hope for a "cure" for HIV infection was reenergized in 2009 when the "Berlin patient" was cured after receiving a stem cell transplant to treat a malignancy [56]. To date, no other individual has achieved a cure, but remarkable progress has been made in transforming HIV from a fatal infection into that of a chronic illness. The single instance of cure provided new insights and new enthusiasm to the field.

**Case Study**

**Case Examples**

| Case 1 | Case 2 |
|---|---|
| A 40-year-old woman presents in active to the obstetrics department of her local hospital. She has not had any prenatal care and admits to having two different sexual partners during the current pregnancy. She tested negative for HIV 2 years ago when she was pregnant with her first child. The patient has never required treatment for a sexually transmitted infection. She delivers a healthy male infant. Postdelivery, blood is collected for routine studies and a rapid HIV test. The rapid HIV test was reported positive later the same day | A 15-year-old female with a prior history of sexual abuse presents to the emergency department with 1 month of fatigue, a 15-pound weight loss, clear vaginal discharge, ulcerations around her labia majora, and headache. Her review of systems was positive for some nuchal rigidity and generalized abdominal pain but negative for photophobia and altered mental status. On physical examination, she had right lower and right upper quadrant abdominal tenderness. Her genital examination showed a clear vaginal discharge and several 1.5 cm ulcerations on her labia. Her neurological examination was normal. Laboratory test results were notable for an absolute lymphocyte count of 200 cells/mm$^3$ and mild elevations in serum hepatic transaminases. Diagnostic testing for HIV, EBV, hepatitis B and C, syphilis, HSV, gonorrhea, and chlamydia was collected. The patient was hospitalized for further management |
| Next steps: (1) maternal, a fourth-generation HIV antibody-antigen test was collected for confirmatory HIV testing | Next steps: The rapid HIV test and the HSV DNA PCR-based test were both reported to be positive. Confirmatory HIV testing was obtained. A lumbar puncture was performed. HSV DNA PCR and antigen-based testing for *Cryptococcus neoformans* were performed on the cerebrospinal fluid |
| Next steps: (2) infant, the newborn was considered a high-risk infant. Postexposure prophylaxis was administered using a three-drug regimen. Blood was collected from the infant to perform a qualitative HIV RNA PCR test | |
| Resolution: Confirmatory testing on the mother, a fourth-generation HIV antibody-antigen test was negative. Additionally, a qualitative HIV RNA PCR was negative on the infant. Once confirmatory tests performed on blood collected from the mother and infant were resulted as negative, the ARV medications were stopped | Resolution: Acyclovir therapy was started as treatment for HSV genital disease and possible aseptic meningitis. Cefoxitin and doxycycline were administered to treat suspected pelvic inflammatory disease.<br>Fourth-generation HIV testing confirmed HIV infection, and ARV medications were prescribed after the cryptococcal antigen test on the cerebrospinal fluid was reported back as negative |
| Highlights: Rapid HIV antibody tests are very sensitive but may have a specificity of only 90%, depending on the method used, leading to a non-negligible rate of false-positive results. In most circumstances, it is appropriate to begin ARV treatment when maternal HIV rapid testing is positive while awaiting confirmatory test results | Highlights: Physical examination and/or laboratory findings that are consistent with a sexually transmitted infection (STI), such as genital HSV infection, should always prompt a careful investigation for other STIs. The physical examination finding of genital ulcerative disease suggestive of HSV infection did not explain the patient's recent weight loss or newly documented lymphopenia |

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## 41.8 Exercises

Please refer to the supplementary information section for answers to these exercises.

1. A 23-year-old male presents with 2 weeks of low-grade fevers, fatigue, and myalgias. On physical examination, he is found to have pharyngeal erythema without exudate, a painful shallow ulcer on the right buccal mucosa, anterior and posterior cervical lymphadenopathy, and a fine erythematous macular rash on his upper chest. He notes that he has a new sexual partner with whom he is using condoms "90% of the time." He reports that he is sexually active with both men and women.

   Of the following, which do you think is the most likely diagnosis?

   A. Infectious mononucleosis
   B. Hodgkin's lymphoma
   C. Streptococcal pharyngitis
   D. Acute retroviral syndrome
   E. Syphilis

2. A rapid antigen test for group A streptococcal infection is negative. A complete blood count with differential shows mild leukopenia but is otherwise normal. A heterophile antibody test for infectious mononucleosis is negative. A rapid plasma regain test is negative. An HIV p24 antigen test is positive. You decide to confirm your diagnosis of acute HIV infection by requesting laboratory testing for the patient's CD4+ T-cell count and HIV viral load. What do you expect the results to look like?

   A. Normal CD4+ T-cell count, low viral load
   B. High CD4+ T-cell count, high viral load

C. Normal CD4+ T-cell count, high viral load
D. Low CD4+ T-cell count, low viral load

3. A 37-year-old man with a past history of syphilis has a positive HIV screening test. His last HIV test was negative 6 months ago. He is asymptomatic and reports that he has felt depressed at times regarding the new diagnosis. He has been sexually active with multiple male partners in the past but recently began a monogamous relationship with an HIV-negative male partner. The patient is worried about transmitting HIV to his new partner. The patient's laboratory evaluation reveals a CD4+ T-cell count of 632 cells/mm$^3$ and an HIV viral load of 32,000 copies/ml. When should he start ART?
   A. As soon as possible
   B. When his CD4+ T-cell count drops below 500 cells/mm$^3$
   C. When his CD4+ T-cell count drops below 350 cells/mm$^3$
   D. When his CD4+ T-cell count drops below 200 cells/mm$^3$

4. A 42-year-old Indian woman presents with generalized fatigue, fevers, night sweats, hemoptysis, and weight loss of 25 lbs over 6 months. A chest radiograph shows hilar adenopathy and a cavitary lesion in the upper lobe of the right lung. Sputum cultures are obtained and grow *Mycobacterium tuberculosis*. During the evaluation she is also found to be infected with HIV. Her CD4+ T-cell count is 32 cells/mm$^3$. Treatment for tuberculosis is initiated. ART with tenofovir alafenamide, emtricitabine, and dolutegravir is also prescribed. The woman's cough, fever, and night sweats initially improve; however, 4 weeks later, she again develops fevers, worsening cough, and shortness of breath. Repeat chest radiography shows new nodular opacities surrounding the cavitary lesion seen initially. The hilar lymphadenopathy appears somewhat more pronounced. Repeat sputum testing is negative for acid-fast bacilli (AFB) by smear and culture. What is the most likely cause of the patient's most recent symptoms?
   A. A drug interaction between two or more of her HIV and tuberculosis medications
   B. An immune inflammatory response syndrome
   C. Multidrug-resistant pulmonary tuberculosis with failed initial therapy
   D. Evolving adenocarcinoma of the lung

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# Essentials of Diagnostic Microbiology

Contents

# Essentials of Diagnostic Microbiology

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## 42.1 Introduction

The modern clinical microbiology laboratory provides diagnostic testing in the areas of bacteriology, virology, mycology, mycobacteriology, parasitology, and often infectious disease serology. In large facilities, these subdisciplines may be physically separated, each with dedicated staff, while smaller facilities provide services within a single laboratory. The breadth of infectious disease testing performed varies considerably between institutions, dependent primarily on available resources, test volumes, the needs of clinical staff, and required turnaround times for results. Samples submitted for testing that is not performed locally, including esoteric or infrequently ordered assays, can be sent to larger regional or national referral laboratories.

Diagnostic microbiology is a complex and ever-changing field of laboratory medicine, so the following is a very broad overview of laboratory diagnostics for infectious diseases. The sources listed at the end of this chapter provide additional detail and are updated on a regular basis. Direct communication with clinical laboratory technologists and their supervisory faculty is always prudent when questions arise about preferred means to test for certain infections, optimal techniques for sample collection, or the interpretation of results they have reported.

## 42.2 Specimen Collection and Transport

It would be a mistake to minimize the importance of the specimen collection step in the infectious disease testing cycle as it is arguably the single most important part of the process. Failure to choose the right specimen and collect it properly can cause delays in obtaining results and can lead to misleading results. Because of the wide variety of biologic specimen types, the devices used in their collection, and the large number of potential pathogens that might be encountered in any given sample, most laboratories provide detailed collection manuals. Nevertheless, it is a good practice to contact the microbiology laboratory prior to specimen collection if unsure and when rare, unusual, or particularly virulent pathogens are suspected.

### 42.2.1 Bacteria and Fungi

There are many bacteria and fungi normally present on the skin and mucous membranes, and certain specimens, e.g., voided urine and expectorated sputum, pass through this milieu as they exit the body. Similarly, samples collected across cutaneous surfaces or mucous membranes are easily contaminated with indigenous (resident) flora. Therefore, a primary objective when collecting specimens for microbiologic analysis is to avoid or minimize this contamination. Swab collection and transport devices, while widely available and convenient to use, are easily contaminated with skin and mucous membrane flora, and the volume of material sampled is quite small. Furthermore, only a fraction of the material absorbed by standard wound fiber swabs is released during the preparation of smears and inoculation of culture media. Sample volume becomes even more of an issue when multiple analyses are requested for a given specimen, frequently necessitating provider input to prioritize testing when a very small amount of sample was collected. For these reasons, aspirates, fluids, and tissue are preferred in most circumstances and provide the best yield and specificity (Fig. 42.1). The most meaningful results are achieved when you adhere to the general principle of "send the specimen, not a swab of the specimen" or, put another way, "send the blob, not the swab".

**Fig. 42.1** Volume comparison between the specimen and a swab of the specimen

The time at which a specimen is collected must also be considered. For example, it is recommended to collect sputum for mycobacterial culture in the morning, when the patient first rises since respiratory secretions, and the organisms in them, are the most concentrated at that time. It is also ideal to collect specimens prior to the use of antimicrobial agents. When possible, it is optimal to collect specimens during the day shift, when dedicated microbiologists are most likely to be available and the laboratory is better staffed. This is especially true for infrequent requests or unusual sample types.

Once collected, the majority of specimen types should either be transported to the laboratory within 2 h or preserved to optimize organism recovery. Some specimens

(e.g., urine) can be preserved by refrigeration for up to 24 h without significant loss of organism viability. Other large-volume body fluids such as pleural fluid may be inoculated into a blood culture bottle, but a portion of the sample should also be sent in a sterile container for the preparation of smears and inoculation of solid media. Swab devices and other systems utilize transport media that preserve organism viability by preventing desiccation and maintaining pH while minimizing multiplication. Viral transport systems also contain antimicrobial agents to prevent bacterial and fungal contamination of tissue cultures.

### 42.2.2 Blood Cultures

The collection of blood cultures deserves special attention due to the potential ramifications of contaminated (false-positive) cultures. The introduction of organisms normally present on the skin (▶ Box 42.1) into the blood culture device can yield misleading results. The growth of skin flora in blood cultures presents diagnostic difficulties, especially in patients with intravascular or prosthetic devices, and cultures drawn through catheters have a higher risk of contamination. Differentiating contaminated cultures from true bacteremia is difficult for both the clinician and the laboratory, primarily since the same organism may be isolated in either situation. Contaminated blood cultures are also a financial drain on the healthcare system, frequently resulting in prolonged hospital stays, increased antimicrobial usage, and additional diagnostic testing. The best way to avoid this interpretive difficulty is to pay strict attention to aseptic technique during blood collection and bottle inoculation. Routinely collecting separate cultures after some variable period does not improve detection of bacteremia arising from an extravascular source and is therefore not necessary. However, collection at timed intervals may be useful for documenting continuous bacteremia in patients with suspected endovascular infections, particularly endocarditis. There is a direct relationship between blood volume and culture positivity; therefore, the single most important factor for the detection of significant bacteremia is the volume of blood cultured. Culture volume thus relates to the number of blood culture sets collected (Table 42.1), with a blood culture set being defined as the volume of blood collected during a single phlebotomy and used to inoculate one or more blood culture bottles. For adults and older children, the general recommendation is to collect 20 mL of blood at each phlebotomy and to inoculate one aerobic and one anaerobic bottle. It is further recommended that a total of three blood culture sets be collected, with each phlebotomy performed at separate venipuncture sites; the use of separate collection sites is critical to the interpretation of blood culture growing organisms commonly found on the skin. For young children, the volume of blood that can safely be collected is dependent on patient weight and clinical condition.

**Table 42.1** Blood culture yield for significant bacteremia

| Type of bacteremia | Number of blood culture sets | Approximate sensitivity[a] |
|---|---|---|
| Endocarditis | 1 | 90% |
| | 2 | 100% |
| Non-endocarditis | 1 | 65% |
| | 2 | 80% |
| | 3 | 96% |

[a]Assumes optimal blood collection volumes; from ref. [3]

### 42.2.3 Viruses

Specimens for viral culture should be collected as soon as possible since, depending on the virus and immune status of the host, cultivable virus may disappear within a few days of symptom onset. Viral viability is maintained during transport and storage using viral transport media (VTM) that contain a buffer system and antimicrobial agents along with added protein to stabilize enveloped viruses. Due to the presence of antimicrobials in VTM, specimens for viral culture must be collected separately from those for other infectious agents.

### 42.2.4 Parasites

Occasionally whole worms or parts of worms (e.g., proglottids, fly larvae) are passed or removed from the body intact (Fig. 42.2). These structures should be sent to the laboratory for identification, and if originating in the gastrointestinal tract, stool should also be submitted for ova and parasite (O&P) examination. Skin scrapings for scabies are collected using a sterile scalpel blade containing a drop of mineral oil and then transferred to a glass slide. Submission of corneal scrapings for *Acanthamoeba* spp. should be coordinated with the laboratory prior to collection.

**Box 42.1 Bacteria Commonly Found on Cutaneous Surfaces**

**Gram positive cocci**
- *Aerococcus* species
- Coagulase-negative staphylococci
- Viridans group streptococci
- Non-hemolytic streptococci
- *Micrococcus* species

**Gram positive rods**
- *Corynebacterium* species and related genera (diphtheroids)
- *Lactobacillus* species
- *Bacillus* species
- *Cutibacterium (Propionibacterium) acnes*

**Fig. 42.2** Botfly larva

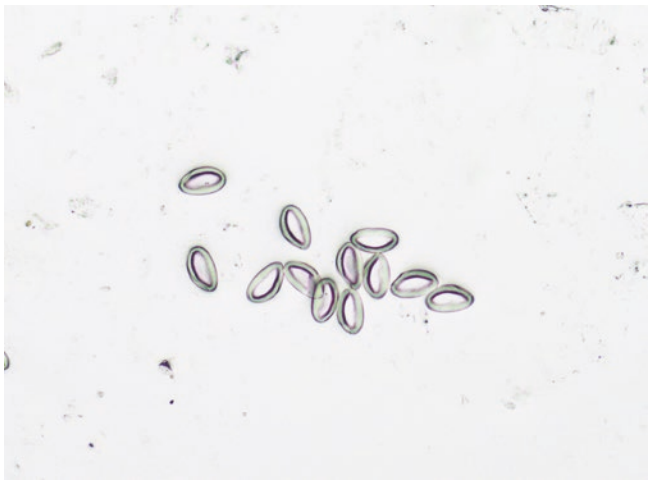

**Fig. 42.3** Pinworm eggs, unstained (100×)

Feces should be collected before the use of barium, mineral oil, or bismuth as these can interfere with laboratory examination. Avoid contamination with water or urine since water may contain free-living organisms that can be mistaken for human parasites and urine may destroy motile protozoans. It is important to note that some parasites, including species of *Giardia*, *Entamoeba*, and *Strongyloides*, are shed into the fecal stream intermittently. For this reason, detection of intestinal parasites by microscopic examination is improved by the submission of three separate samples, preferably collected every other day. Unpreserved liquid stool may be examined by direct microscopy for motile protozoans, but the sample must be sent to the laboratory within 30 min of passage, or the organisms will disintegrate or stop moving, making them nearly impossible to detect. Whenever transport is delayed, specimens must be preserved, most frequently using a two-vial system of formalin and polyvinyl alcohol (PVA). Formalin-preserved specimens are used for concentration procedures, and PVA-preserved material is used for the preparation of stained smears.

The laboratory detection of *Enterobius vermicularis* (pinworms) requires an approach different than that for other intestinal parasites. Since eggs are deposited on the perianal skin by migrating females, stool is not an ideal specimen for diagnostic purposes. To detect the eggs of this worm, commercial paddles with sticky surfaces are pressed onto the anal folds immediately after arising and before bathing or defecation. Eggs adhere to the sticky surface of the paddle and are readily detected by microscopic examination (Fig. 42.3).

In many parts of the world, the preferred specimen for the detection of blood parasites is a drop of capillary blood from a finger or earlobe stick. Far more common in nonendemic countries is the use of EDTA anticoagulated venous blood. A single specimen for microscopic examination does not rule out the presence of blood parasites, including species of *Plasmodium* and *Babesia*, since their presence in the bloodstream can fluctuate. For this reason, optimal sensitivity is achieved through the examination of at least three samples collected 8–12 h apart. Depending on the species, the presence of microfilaria can also show marked periodicity in blood, so the time of specimen collection is important (Table 42.2).

**Table 42.2** Blood collection times for the detection of microfilaria

| Parasite | Optimal collection time |
|---|---|
| *Loa loa* | 10 AM–2 PM |
| *Brugia, Wuchereria* | After 8 PM |
| *Mansonella, Onchocerca* | Any time |

### 42.2.5 Molecular Assays

Because nucleic acid amplification does not require viable organisms for detection, transport issues are greatly eased. The main concern for these assays is to prevent the nucleic acids in the sample from degrading prior to performing the assay. As a rule, refrigeration or freezing is acceptable, but sample requirements vary and often require proprietary collection and transport devices.

## 42.3 Direct Detection of Microorganisms

The microscopic evaluation of stained or unstained preparations of clinical specimens provides a rapid means of direct microorganism detection that may provide important early clues about an infectious process. The simplest type of direct examination is the wet mount, where an aliquot of liquid specimen, mixtures of specimen and saline, or concentrated sediment is observed using bright-field or phase-contrast

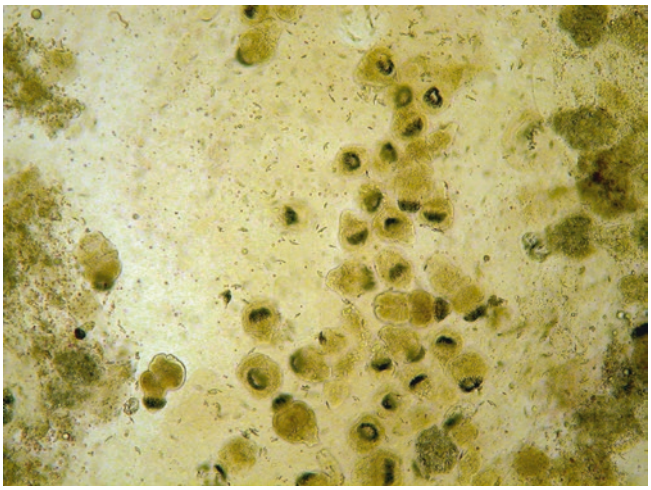

**Fig. 42.4** *Echinococcus* protoscolices (hydatid sand), direct wet mount of hydatid cyst fluid (100×)

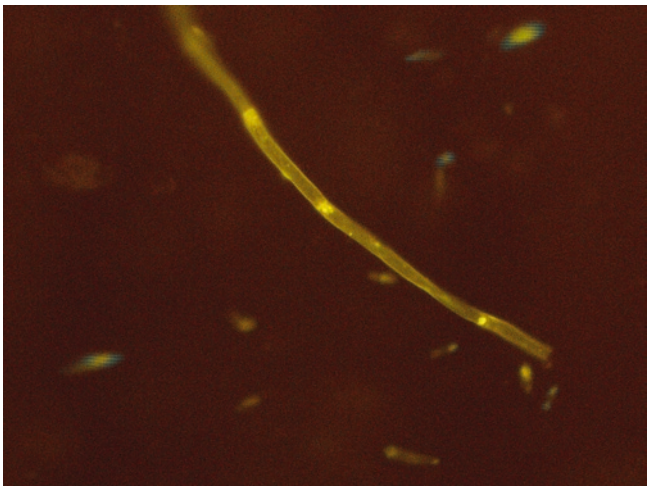

**Fig. 42.6** Fungal hyphae, calcofluor-white (400×)

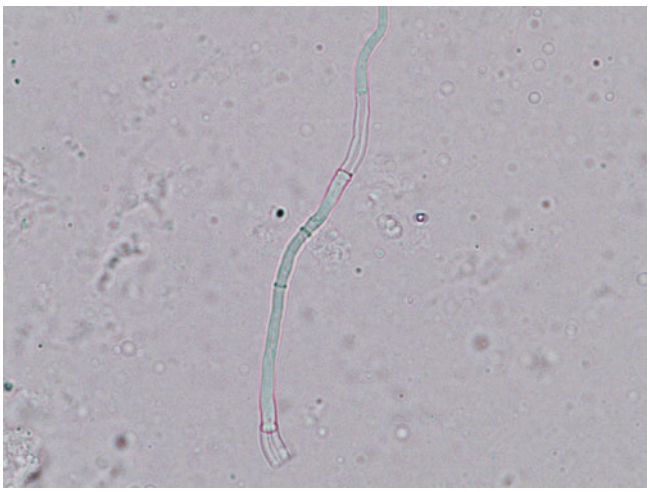

**Fig. 42.5** Fungal hyphae, KOH (100×)

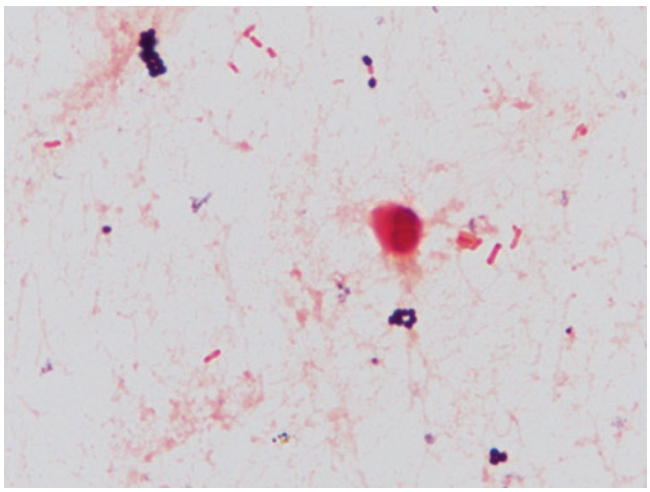

**Fig. 42.7** Sputum, Gram stain (1000×)

microscopy (Fig. 42.4). Common applications of this method include the examination of vaginal secretions for *Trichomonas vaginalis* and liquid stool for motile protozoans. Samples are typically mixed with KOH alone (Fig. 42.5) or KOH plus the fluorochrome calcofluor white (Fig. 42.6) prior to examination for fungi to clear the background and make yeast and hyphae more visible. Although not as commonly available as bright-field microscopy, examination by dark-field microscopy can be used for the direct detection of spirochetes in various specimens including the demonstration of *Treponema pallidum* in material collected from chancres.

A variety of stains may be used to visualize bacteria, but the two most common are the Gram stain and acid-fast stain. The Gram stain is performed by flooding smears of clinical material on glass slides with a mixture of the primary stain (crystal violet) and Gram's iodine, which facilitates the binding of crystal violet to the peptidoglycan component of bacterial cell walls. After the slides are rinsed, the smear is overlaid with a decolorizer, rinsed again, and flooded with the counterstain safranin. The decolorization step distinguishes bacteria into two groups: those that retain crystal violet after exposure to the decolorizer (Gram positive) and those that are decolorized and subsequently stained by safranin (Gram negative, (Fig. 42.7)). The retention or loss of crystal violet reflects differences in the physical and chemical composition of the cell wall between the two types of bacteria. Although designed to detect and differentiate bacteria, yeast may also be observed and usually stain Gram positive or mottled purple and pink (Fig. 42.8).

Aside from the Gram reaction, other observations that can be made for bacterial cells include their size, shape (rod, coccus, coccobacillus), and arrangement (pairs, chains, clusters, Fig. 42.9). Host cells including leukocytes and epithelial cells are visible in Gram-stained smears, and their presence is reported along with any observed microorganisms. Gram-stained smears can also be used to assess the quality of a sample, and most laboratories screen expectorated sputum prior to routine bacterial culture (Fig. 42.10).

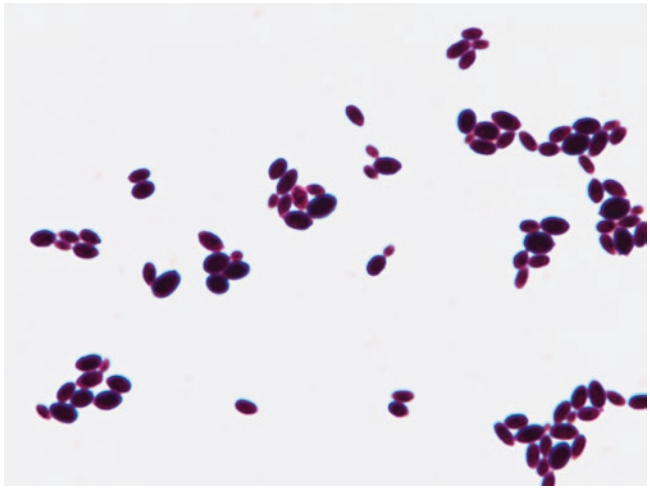

**Fig. 42.8** Budding yeast, Gram stain (1000×)

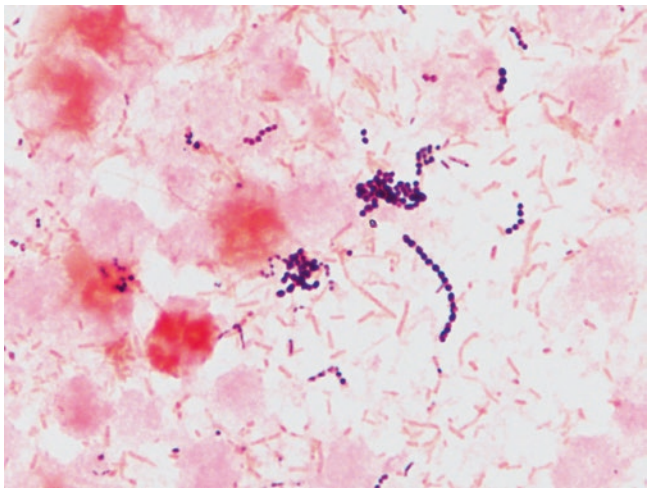

**Fig. 42.9** Body fluid, Gram stain (1000×)

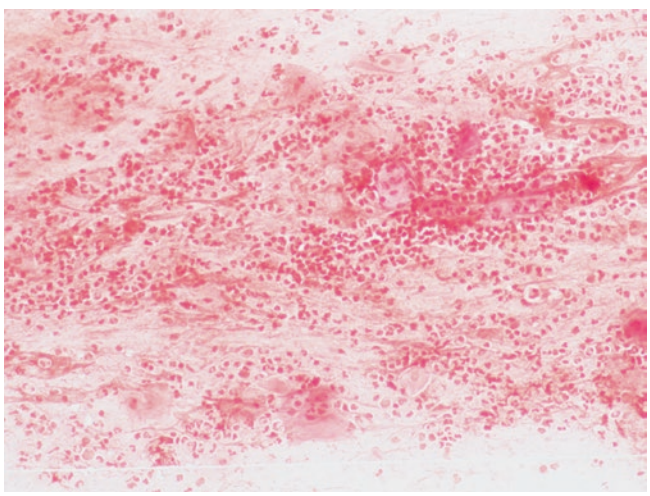

**Fig. 42.10** Quality sputum, Gram stain (100×)

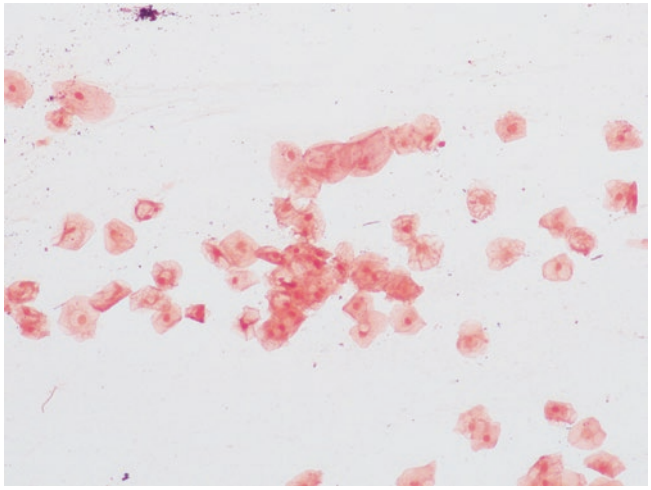

**Fig. 42.11** Poor-quality sputum, Gram stain (100×)

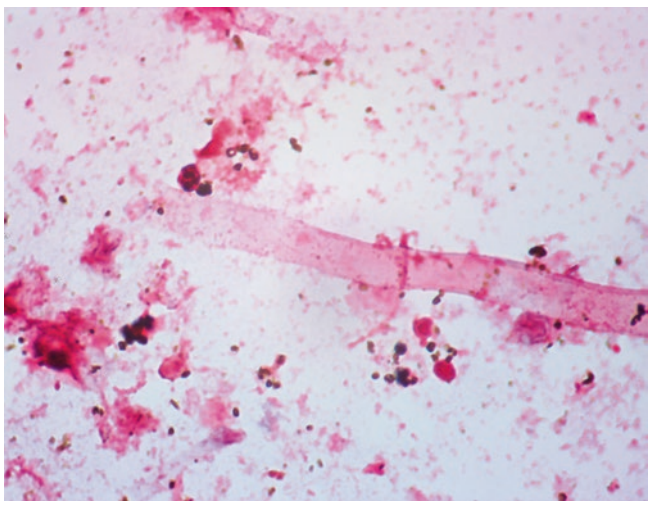

**Fig. 42.12** Hyphal fragment, Gram stain (1000×)

If the specimen contains an excessive number of squamous epithelial cells (Fig. 42.11), it is considered representative of saliva, not sputum, and is not cultured.

Deceptively simple to perform, the interpretation of Gram-stained smears can be challenging. For example, some Gram positive organisms including *Streptococcus pneumoniae*, *Bacillus* species, and certain species of *Clostridium* can stain Gram negative in direct smears. Likewise, Gram negative organisms such as *Acinetobacter* spp. may falsely appear Gram positive. The size, shape, and staining properties of bacteria can be affected by antimicrobial use. Gram negative organisms may be particularly difficult to discern against the pink background of highly proteinaceous specimens.

Despite its utility, the Gram stain has a few limitations. Some clinically relevant types of bacteria either do not stain well (e.g., mycobacteria) or are not stained at all (e.g., *Mycoplasma* species), and fungal hyphae (Fig. 42.12) are also not reliably detected. The sensitivity of the Gram stain is also limited, requiring roughly $10^5$ organisms/mL of sample

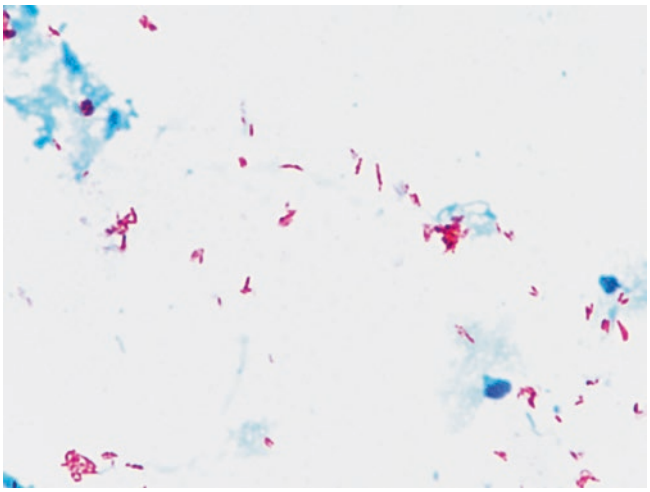

**Fig. 42.13** *Mycobacterium*, Kinyoun acid-fast stain (1000×)

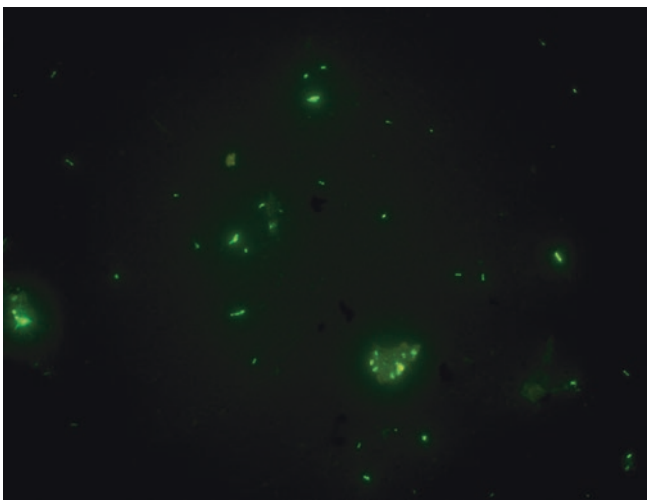

**Fig. 42.14** *Mycobacterium*, auramine acid-fast stain (400×)

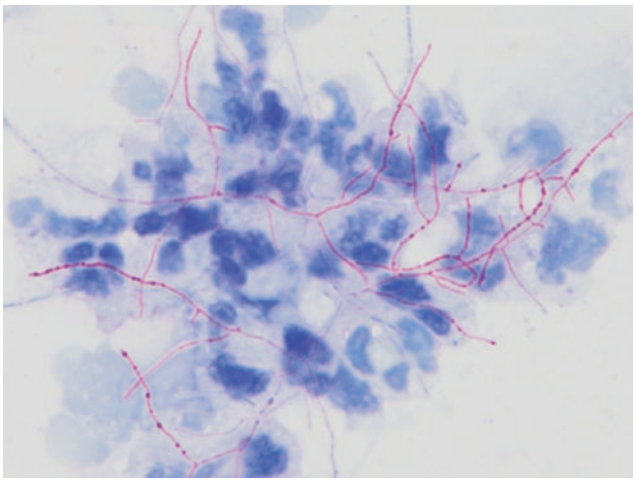

**Fig. 42.15** *Nocardia* in sputum smear, modified acid-fast stain (1000×)

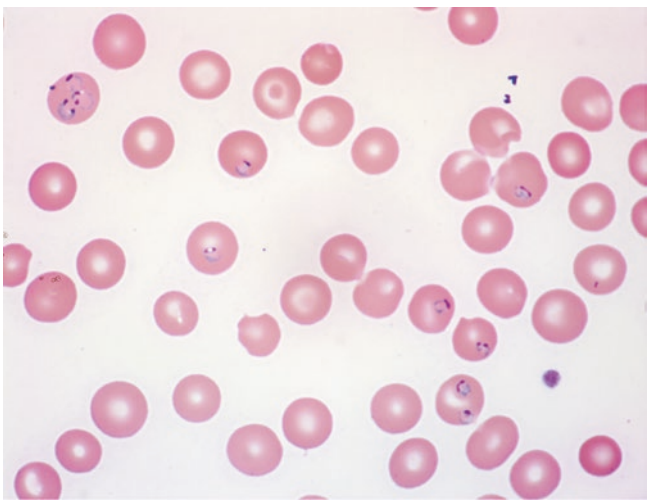

**Fig. 42.16** *Plasmodium falciparum* in thin blood film, Wright's stain (1000×)

for visualization, and while the Gram reaction, shape, and arrangement may suggest the presence of particular pathogens, a definitive identification of observed organisms is not possible using the Gram stain alone.

The cell walls of mycobacteria contain waxes and long-chain fatty acids making them relatively impervious to dyes, so the use of heat or phenol is required for staining to occur. Once stained, they are difficult to decolorize, even with acid-alcohol, and are therefore described as being acid-fast. Classical acid-fast stains (Ziehl-Neelsen and Kinyoun) employ carbolfuchsin as the primary stain and are observed using bright-field microscopy. Acid-fast organisms stain red due to retention of the basic fuchsin, and other organisms are blue, the color of the counterstain (Fig. 42.13). Fluorescent stains use the fluorochrome dye auramine with or without rhodamine, and potassium permanganate as the counterstain. When viewed by fluorescence microscopy, acid-fast organisms appear as bright fluorescent rods against a dark background (Fig. 42.14). The sensitivity of acid-fast stains varies by specimen type and extent of disease but is highest for respiratory secretions collected early in the morning. Detection in liquified and concentrated specimens is estimated to require approximately $10^4$ bacilli per milliliter of sputum. Acid-fast stains do not distinguish between *Mycobacterium tuberculosis* and other mycobacteria. The modified acid-fast stain, useful for detecting *Nocardia* and coccidian oocysts, is a variant of the Kinyoun stain that uses a less harsh decolorizer (Fig. 42.15).

Giemsa, Wright-Giemsa, and Wright's stains are primarily used to demonstrate the presence of *Plasmodium* species (Fig. 42.16), *Babesia* species (Fig. 42.17), and other parasites in thin and thick blood films. Thin films are prepared the same way smears are made to determine differential cell types on a complete blood count. Doing so allows the microbiologist to identify and speciate the parasite based on its morphologic features. For thick smears, 1–2 drops of blood are spread onto a slide and lysed in buffer prior to staining. Because more blood is used over a smaller area, thick films are reportedly up to 20 times more sensitive than thin films

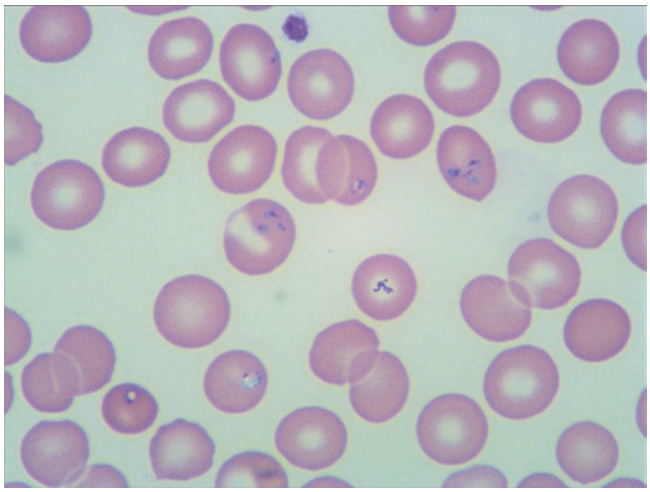

**Fig. 42.17** *Babesia* in thin blood film, Wright's stain (1000×)

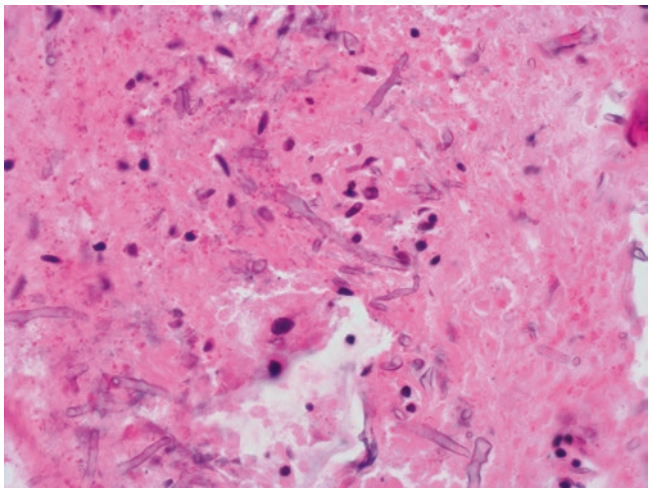

**Fig. 42.19** Tissue section with mucormycete hyphae, H&E (400×)

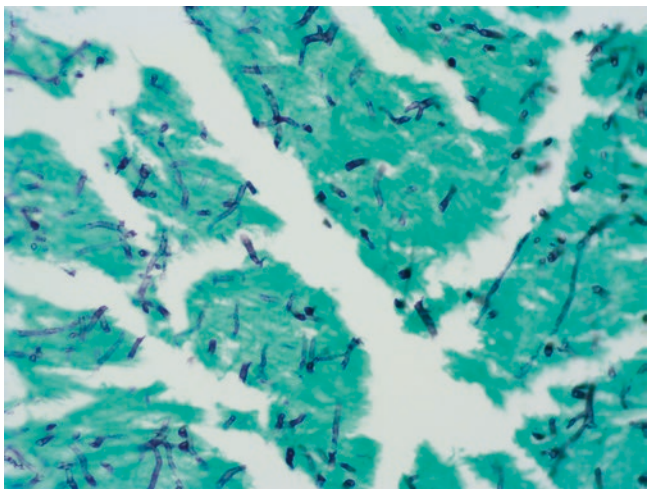

**Fig. 42.18** Tissue section with fungal hyphae, Gomori methenamine silver stain (GMS; 400×)

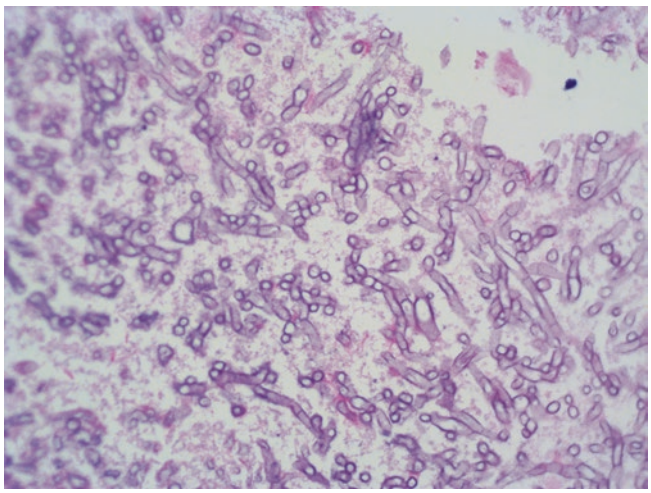

**Fig. 42.20** Tissue section with hyalohyphomycete hyphae, H&E (400×)

in identifying the presence of a blood parasite, but the processing steps cause morphologic distortions making speciation unreliable for *Plasmodium*. Detection of microfilaria may require concentration of specimens prior to analysis.

In the histopathology laboratory, the hematoxylin and eosin (H&E) stain is used routinely as are special-purpose stains including Gram's, acid-fast, periodic acid-Schiff (PAS), silver, and mucicarmine. The primary advantage of histopathologic examination for infectious diseases is the ability to visualize the host inflammatory response, particularly when using H&E. Different patterns of inflammation may suggest particular pathogens or groups of pathogens and therefore drive the use of additional, more specialized stains. For example, a granulomatous reaction requires further staining with the tissue acid-fast stain to detect mycobacteria, and either PAS or a silver stain would be used to detect fungi (Fig. 42.18). If yeast forms are seen, tissue sections can be stained with mucicarmine to demonstrate the capsule of *Cryptococcus neoformans*. A relatively common challenge for the histopathologist is the identification of fungal hyphae. Definitive identification of a mold cannot be made based solely on morphological grounds, but placement into broad categories of fungi is usually possible. For example, hyphae that are broad and ribbon-like with sparse septation and perpendicular branching are characteristic of mucormycetes (zygomycetes) such as *Rhizopus* species (Fig. 42.19). Narrower hyphae with frequent septation and acute angle branching are characteristic of hyalohyphomycetes (e.g., *Aspergillus* species, Fig. 42.20), and pigmented hyphae are suggestive of a dematiaceous (dark colored) mold. Acute inflammation, seen in bacterial infection and in the early stages of mycobacterial, fungal, and parasitic diseases, prompts the use of the tissue Gram stain. Although useful, this stain can be challenging to interpret, and silver stains are required to visualize some types of bacteria including spirochetes. Viral inclusions (Fig. 42.21) and occasionally parasites may also be seen in H&E-stained sections. Immunochemical stains for *Helicobacter pylori*, *Toxoplasma gondii*, and certain herpesviruses are also available.

A range of bacterial, fungal, viral, and parasite antigen detection tests have been developed for diagnostic use

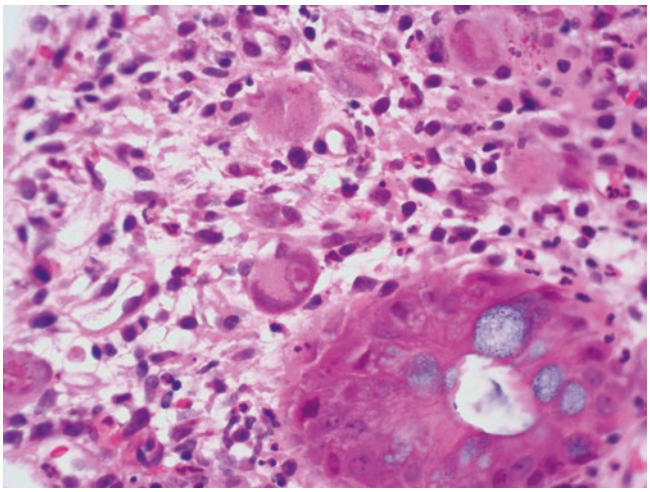

**Fig. 42.21** Tissue section with cytomegalovirus inclusion, H&E (400×)

**Box 42.2 Common Antigen-based Diagnostic Laboratory Tests for Agents of Infectious Disease**

**Bacteria**
- *Campylobacter jejuni/C. coli*
- *Clostridium difficile* toxins A and B, glutamate dehydrogenase (GDH)
- *Helicobacter pylori*
- *Legionella pneumophila* (serogroup 1)
- Shiga-like toxins
- *Streptococcus pneumoniae*
- *Streptococcus pyogenes*

**Viruses**
- Hepatitis B virus
- Human immune deficiency virus type 1
- Influenza viruses A and B
- Respiratory syncytial virus
- Rotavirus

**Fungi**
- Beta-D-glucan
- *Blastomyces dermatitidis*
- *Coccidioides*
- *Cryptococcus neoformans*
- Galactomannan
- *Histoplasma capsulatum*
- *Pneumocystis jirovecii*

**Parasites**
- *Cryptosporidium* species
- *Entamoeba histolytica/E. dispar*
- *Giardia* species
- *Plasmodium* species
- *Trichomonas vaginalis*

(▶ Box 42.2). Target antigens may be integral to whole organisms, expressed by infected cells, or released as free antigens or toxins. Depending on the assay, antigen tests have been designed for use with diverse specimen types including blood, urine, stool, throat and vaginal swabs, and respiratory

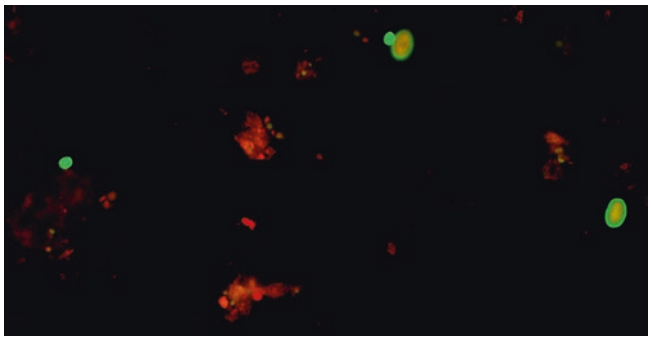

**Fig. 42.22** *Giardia* cysts and *Cryptosporidium* oocytes, immunofluorescence (400×)


**Fig. 42.23** *Legionella pneumophila* serogroup 1 urine antigen test, immunochromatography

secretions. Multiple detection formats have been described, but the most common are traditional and rapid variations of enzyme immunoassay, latex agglutination, immunofluorescence (Fig. 42.22), and immunochromatography (Fig. 42.23). Antigen tests can provide useful information much earlier than culture, and many have been designed to be performed in the point of care setting, further increasing their utility. However, these advantages must be weighed against the limited sensitivity for some of these assays when compared to culture and nucleic acid amplification. Due to this lack of sensitivity, a negative antigen result often requires further testing using a more sensitive method. One common example is the general recommendation to perform culture

**Table 42.3** Nucleic acid amplification assays

| Amplification assay | Amplification category | Amplification product | Example applications |
|---|---|---|---|
| Polymerase chain reaction (PCR) | Target | DNA | Influenza A virus, methicillin-resistant *Staphylococcus aureus* |
| Transcription-mediated amplification (TMA) | Target | RNA | HIV-1 RNA, *Trichomonas vaginalis* |
| Helicase-dependent amplification (HDA) | Target | DNA | *Clostridium difficile*, varicella-zoster virus |
| Hybrid capture assay (HCA) | Signal | DNA/RNA hybrid | Human papillomavirus |
| Strand displacement amplification (SDA) | Target | DNA | *Neisseria gonorrhoeae*, *Chlamydia trachomatis* |
| Loop-mediated amplification (LAMP) | Target | DNA stem-loop structures | *Mycoplasma pneumoniae*, *Bordetella pertussis* |
| Cleavase-invader technology | Signal | Fluorescent probe cleavage fragment | Human papillomavirus |

for throat specimens that test negative with a rapid antigen test for group A *Streptococcus* (*S. pyogenes*). Similarly, the use of cerebrospinal fluid (CSF) bacterial antigen tests is now discouraged since they are no more sensitive than an appropriately performed Gram stain. Antigen-based tests for the detection of *Clostridium difficile* toxins in stool and respiratory viruses in nasopharyngeal specimens are also being replaced with more sensitive assays.

Nucleic acid tests (NAT), whether nonamplified probes or nucleic acid amplification tests (NAAT), are generally employed for the detection of antimicrobial resistance markers, organisms that are slow, difficult, or hazardous to grow, to determine the quantity of virus circulating in the bloodstream (viral load) and for their improved sensitivity and speed compared to conventional methods. In nonamplified probe assays, labeled DNA or RNA molecules are added to a test sample with a positive signal being generated if complementary sequences are present. Although less sensitive than amplification assays, nonamplified probe tests are still frequently used to detect *Gardnerella vaginalis*, *Trichomonas vaginalis*, and *Candida* species in vaginal secretions and for the identification of bacteria and yeast from positive blood cultures. Similar probe technology can be used to detect infectious agents in sections of fixed or frozen tissue as well as cytologic preparations.

Nucleic acid amplification tests are categorized as either signal amplification or target amplification (Table 42.3) assays. In signal amplification assays, no new nucleic acid is created, but a signal resulting from nucleic acid hybridization is amplified manyfold. In contrast, target amplification assays result in the generation of many copies of nucleic acid if the specific target sequence is present in the patient's sample. Both laboratory-developed and commercial assays have found broad application and may be either qualitative or quantitative. Originally designed as batch tests that required significant expertise to perform, advances in NAAT technology and the simultaneous simplification of testing protocols have placed the ability to perform many of these assays within the reach of any clinical laboratory. Several current platforms utilize single-use closed devices containing all the necessary components for nucleic acid isolation, amplification, and detection. These sample-to-result assays are easy to perform, and most provide results in about an hour (Figs. 42.24 and 42.25). The most recent trend in molecular microbiology has been the development of highly multiplexed syndromic panels capable of rapidly detecting both resistance determinants and multiple potential etiologies of gastroenteritis, respiratory disease, meningitis/encephalitis, and bacteremia. Despite their advantages, it is important to recognize that molecular assays are neither 100% sensitive nor specific, performance can vary significantly in different test populations, culture is required to obtain isolates for antimicrobial susceptibility testing, and testing is generally discouraged as a test of cure since both live and dead organisms are detected.



## 42.4 Culture of Microorganisms

### 42.4.1 Bacteria and Fungi

Most bacteria and fungi can be cultured in vitro when appropriate conditions are supplied. If an organisms' nutritional and environmental requirements are met, they will multiply to the point where visible colonies are formed (solid media) or turbidity develops (liquid media). No single medium supports the growth of all potential pathogens, so myriad solid and liquid media have been developed to satisfy a wide range of nutritional requirements, but relatively few are used


**Fig. 42.24** Cepheid GeneXpert® MTB/RIF real-time PCR assay cartridge


**Fig. 42.25** BioFire FilmArray® Respiratory Pathogen Panel pouch

routinely (Table 42.4). Basic components for solid media include sources of carbon and nitrogen, water, and agar, but many organisms require additional growth factors such as vitamins, fatty acids, trace metals, or blood components. For example, the isolation of *Haemophilus* spp. requires supplementation of culture media with hemin and NAD. The media used by clinical laboratories may be categorized as nonselective, selective, or differential. Nonselective media support the growth of most clinically relevant organisms and do not contain selective agents, while selective media contain dyes, antimicrobials, bile salts, or other factors allowing the growth of some organisms but slowing or preventing the growth of others. Differential media typically contain substrates that when metabolized lead to acid production and corresponding color change by a pH indicator (Fig. 42.26); newer media may contain chromogenic dyes that change color when specific enzyme activity is present (Fig. 42.27). Due to the variety of bacteria and fungi encountered in clinical specimens, multiple media must be used to isolate a range of potential pathogens; the selection of media to be used is based upon both the specimen type and the common pathogens associated with that anatomic site.

Liquid media are used primarily for the cultivation of blood and for the selective enrichment of specific organisms prior to subculture onto solid media. Selective broth enrichment is notably used for the isolation of *Streptococcus agalactiae* from anovaginal specimens late in pregnancy. The components of liquid media are similar to solid media except for the lack of a solidifying agent.

An appropriate incubation environment – temperature, atmosphere, and humidity – must also be provided to cultivate microorganisms. Since most human pathogens grow best at or near body temperature, media are usually incubated between 35 °C and 37 °C. However, some pathogens either grow optimally or grow better than most other organisms at different temperatures. For example, incubation at 42 °C aids in the selective isolation of *Campylobacter jejuni*, and incubation at 25 °C is used for the cultivation of molds. Certain fungi (e.g., *Histoplasma capsulatum*) exhibit thermal dimorphism, growing as yeast at body temperature and as a filamentous mold at lower temperatures.

Bacteria have different relationships to oxygen (Table 42.5). Many laboratories utilize commercial bag and jar systems to generate anaerobic and microaerophilic atmospheres, while larger laboratories may use a specialized incubator called an anaerobic chamber (glove box) for the cultivation of anaerobes. Although most obligate aerobes and facultative anaerobes will grow in an ambient air atmosphere (~21% oxygen), the growth of certain organisms is improved

**Table 42.4** Common culture media

| Medium | Type | Principle use |
|---|---|---|
| Blood agar | Nonselective | Isolation of non-fastidious organisms; detection of hemolytic activity |
| Buffered charcoal-yeast extract agar | Nonselective | Isolation of *Legionella* and *Nocardia* species |
| *Campylobacter* agars | Selective | Selective isolation of *Campylobacter* species |
| Chocolate agar | Nonselective | Isolation of fastidious organisms including *Haemophilus* and pathogenic *Neisseria* species |
| Colistin-nalidixic acid agar | Selective | Selective isolation of Gram-positive bacteria |
| Hektoen enteric agar | Selective, differential | Selective isolation and differentiation of *Salmonella* and *Shigella* from stool samples |
| Inhibitory mold agar | Selective | Isolation of most pathogenic and saprobic fungi from non-sterile sites |
| LIM broth | Selective | Selective enrichment of *Streptococcus agalactiae* |
| Löwenstein-Jensen media | Selective | Isolation of mycobacteria |
| MacConkey agar | Selective and differential | Selective isolation of non-fastidious Gram-negative rods; detection of lactose fermentation |
| MacConkey sorbitol agar | Selective and differential | Selective isolation of 0157:H7 strains of *E. coli* from stool samples |
| Middlebrook agar | Selective | Isolation of mycobacteria |
| Selective brain heart infusion agar | Selective | Isolation of most pathogenic fungi |
| Thayer-Martin agar | Selective | Selective for pathogenic *Neisseria* |
| TCBS agar | Selective, differential | Selective isolation and differentiation of *Vibrio* from stool samples |

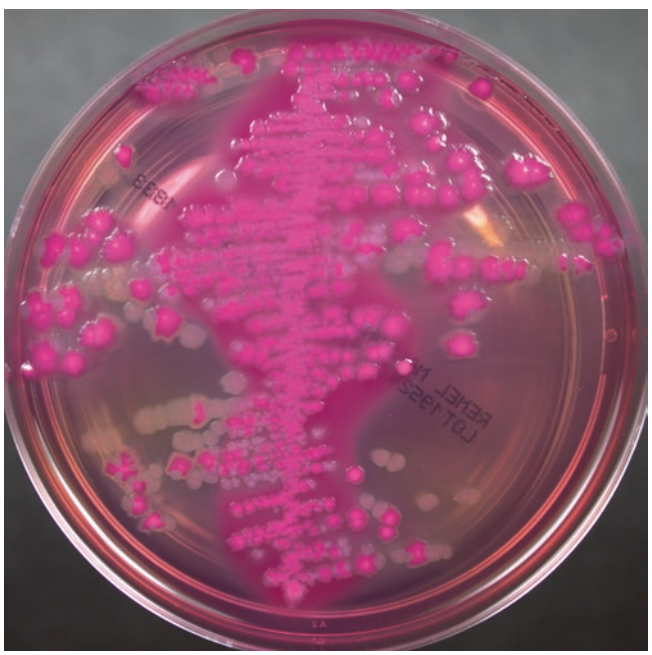

**Fig. 42.26** Lactose-fermenting and nonlactose-fermenting colonies, MacConkey agar

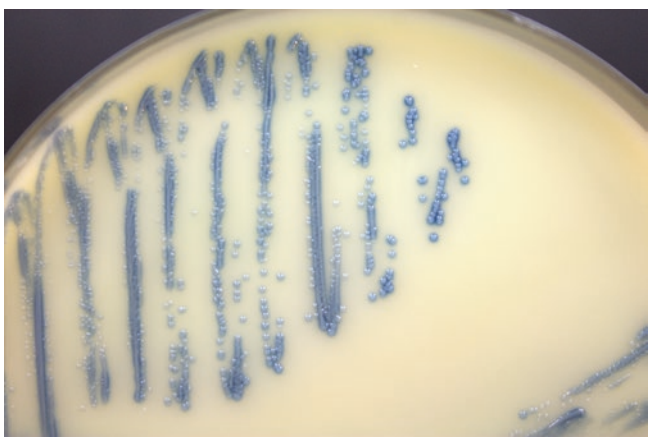

**Fig. 42.27** Methicillin-resistant *Staphylococcus aureus*, Spectra™ MRSA agar

through the addition of 5–10% $CO_2$. Lastly, an adequately humid environment provides the moisture required for metabolic activities and prevents drying of the culture media.

With only a few exceptions, cultures are performed qualitatively or semiquantitatively. An unmeasured aliquot

**Table 42.5** Bacterial relationships to oxygen

| Category | Required atmosphere | Examples |
|---|---|---|
| Obligate aerobe | Approximately 21% oxygen | *Pseudomonas aeruginosa*, mycobacteria |
| Facultative anaerobe | Aerobic or anaerobic | *Staphylococcus aureus*, *Escherichia coli* |
| Microaerophile | Approximately 5% oxygen | *Campylobacter jejuni* |
| Obligate anaerobe | <5% oxygen | *Bacteroides*, *Fusobacterium* |

of material is deposited onto the agar and spread across the surface using a sterile inoculating loop or is placed into a broth-containing vessel. Spreading with a loop effectively dilutes the material and allows for the formation of isolated colonies. Depending on the specimen type, samples may be concentrated by centrifugation (e.g., body fluids), ground (tissue), or otherwise manipulated prior to media inoculation. Following incubation, the relative amount of growth in semiquantitative cultures is reported as rare (1+), few (2+), moderate (3+), or many (4+); note that the growth in liquid media cannot be quantitated. For quantitative cultures, a defined amount of specimen is used for inoculation, and the resulting colonies are counted to determine the number of organisms that were present in the original sample; urine is the most common specimen type cultured quantitatively. The duration of culture incubation varies by specimen type and the potential pathogens sought, ranging from 18–24 h for routine urine cultures to 6–8 weeks for mycobacteria.

#### 42.4.1.1 Blood Cultures

Most clinical laboratories employ automated systems for the culture of blood. Several such systems are available, but they all utilize bottles containing nutrient-rich broth media that support the growth of a wide variety of bacteria and yeasts. Different bottles are available for the culture of aerobic and anaerobic bacteria (Fig. 42.28), mycobacteria, and fungi as are bottles optimized for use with the smaller volumes of blood collected from young children (Fig. 42.29). The anticoagulant used for blood cultures is sodium polyanethol sulfonate (SPS) which also has anti-phagocytic and anticomplement activity. The area above the liquid surface (headspace) contains a mixture of either oxygen and carbon dioxide in aerobic bottles or nitrogen and carbon dioxide in anaerobic bottles. Specialized bottles contain activated charcoal or binding resins to help neutralize the activity of antimicrobials introduced with the blood sample.

Once placed into the instrument in the laboratory, blood bottles are continuously monitored for evidence of bacterial growth. The specific means of growth detection varies between platforms but relies on either directly detecting the $CO_2$ produced by metabolizing organisms or by detecting changes in headspace pressure caused by the production and/or consumption of $CO_2$ or $N_2$ (manometry). Routine aerobic and


**Fig. 42.28** Aerobic and anaerobic blood culture bottles

anaerobic blood cultures are typically incubated for 5 days, while those for fungi and mycobacteria are observed over a period of 4 and 6 weeks, respectively. Incubation of routine blood cultures longer than 5 days is rarely indicated since modern blood culture media detect even the agents historically associated with culture-negative endocarditis (*Haemophilus* species, *Aggregatibacter* species, *Cardiobacterium* species, *Eikenella corrodens*, and *Kingella* species; HACEK) within this period. Although separate bottles for fungi are available, it is useful to note that *Candida* species grow well in routine blood culture bottles.

Lysis centrifugation is a manual method for culturing blood that many laboratories use for the isolation of fungi and mycobacteria. Blood is collected into tubes containing SPS and the lytic agent saponin. Saponin lyses blood cells to release both nutrients and intracellular organisms. Organisms in the lysed specimen are concentrated by centrifugation, and the sediment is plated onto solid media. The primary advantages of this system are that intracellular organisms are released making them easier to detect and the media and incubation conditions can be tailored to the pathogens sought.

### 42.4.2 Viruses

Even with the wide availability of molecular assays in diagnostic virology, larger laboratories frequently retain culture


**Fig. 42.29** Blood culture bottles for mycobacteria/fungi and young children

capability and some viruses are detectable within 2-3 days. Culture remains useful for samples that have not been validated for molecular tests, when an isolate is needed for susceptibility testing and for strain typing. However, not all viruses are cultivable by clinical laboratories, notable examples being human papillomavirus and the hepatitis viruses.

Because viruses are obligate intracellular parasites, a eukaryotic host cell must be provided for their propagation. Two types of viral culture are used in clinical laboratories, conventional and shell vial (Fig. 42.30), both employing host cells grown on glass or plastic surfaces. The cultured cells form a layer one cell thick (monolayer) and are bathed in media containing nutrients, a buffer system, and antimicrobial agents to maintain monolayer health. Antimicrobials are required to suppress the growth of contaminating bacteria and fungi that can destroy the monolayer and mask the presence of virus.

The multiple types of cells that may be used for viral culture can be grouped into three general categories: primary cells (e.g., primary monkey kidney), derived directly from mammalian tissues and containing mixed euploid cell types, diploid cell (e.g., MRC-5) subculture lines consisting primarily of euploid fibroblasts (Fig. 42.31), and continuous cell lines (e.g., A549), derived from neoplasms and containing more than 25% aneuploid cells. As with bacterial culture, no one cell type supports the growth of all clinically relevant viruses, so the types of cells used when viral cultures are performed are based upon the specimen source and potential virus etiologies.

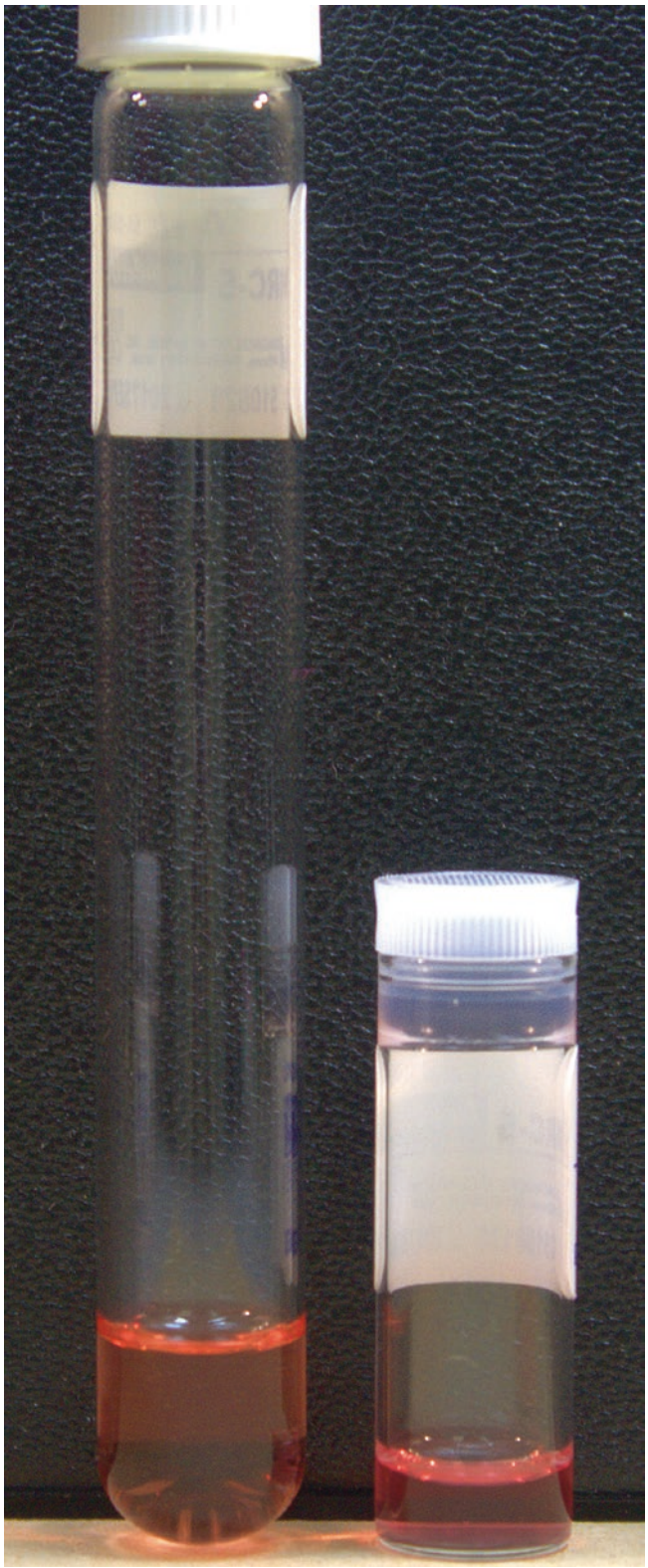

**Fig. 42.30** Conventional and shell vial cell culture tubes

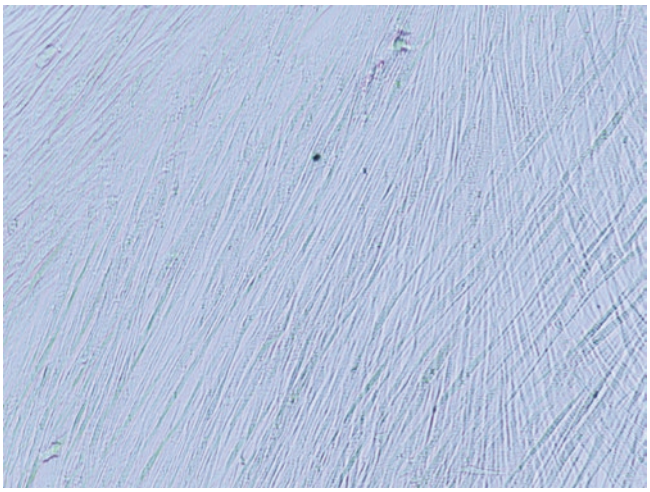

**Fig. 42.31** Human diploid fibroblast monolayer, uninfected (100×)

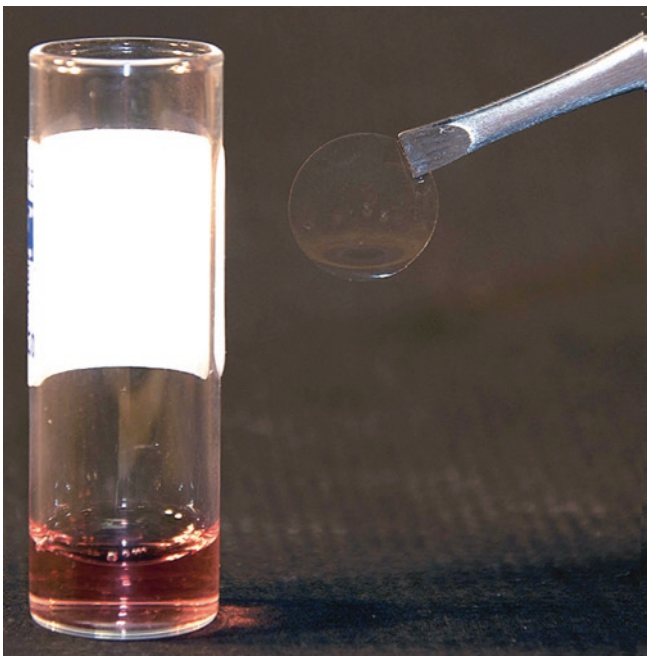

**Fig. 42.32** Shell vial monolayer

For conventional viral culture, specimens in viral transport medium are layered onto monolayers from which the cell culture medium has been removed. Following a short incubation period to allow virus to attach to the host cells, fresh medium is added, and the cultures are incubated at 35 °C. The duration of incubation varies from a week for most viruses to 28 days for slower-growing organisms such as cytomegalovirus.

Shell vial culture uses the same types of eukaryotic host cells, but unlike conventional cell cultures, the monolayer is formed on round glass coverslips contained in flat-bottomed vials (Fig. 42.32). After the vials are inoculated with clinical material, they undergo a low-speed centrifugation and are then incubated for 1–3 days prior to staining the monolayer for the presence of viral antigen.

## 42.5 Identification of Microorganisms

### 42.5.1 Bacteria and Yeasts

Once visible growth occurs, culture plates are evaluated for different colony morphologies. A skilled microbiologist can not only discern multiple colony types representing different organisms but can also recognize morphologies representing indigenous flora or suggestive of potential pathogens. Organisms selected for further evaluation must first be separated from other organisms in pure culture, which frequently occurs on the primary culture plates but may require subculture to fresh media. Identification begins by observing the pattern and rate of growth on different media, the atmosphere required for optimal growth, the macroscopic features of the colonies such as hemolysis on sheep's blood agar or the presence of pigmentation, and the isolate's Gram stain morphology. Rapid spot tests for catalase, oxidase, and indole are also often performed to strengthen a presumptive identification or to aid in the selection of subsequent procedures.

#### 42.5.1.1 Phenotypic Identification

The approach to isolate identification can vary between laboratories and depends on the nature of the organism, available methods, and local resources. Some organisms can be accurately identified to species based upon macroscopic and microscopic morphology with or without supplemental spot tests. For example, oxidase-positive Gram negative rods producing characteristic colonies (Fig. 42.33) and a sweet, grape-like odor are readily identified as *Pseudomonas aeruginosa.* Similarly, the use of chromogenic agars allows for the direct identification of select enteric Gram negative rods and yeast based upon colony color. Other organisms may be identified using rapid commercial identification kits such as agglutination tests for *Staphylococcus aureus* and Lancefield typing reagents for beta-hemolytic streptococci.

For many isolates, more extensive testing is required. Most laboratories use commercial manual and automated identification systems for this purpose. These systems employ miniaturized panels of biochemical substrates measuring carbon and nitrogen source utilization, enzymatic activity, and a variety of other properties of the organism (biochemical phenotyping). The resulting phenotypic profile is then compared to computerized databases of known profiles to determine isolate identity.

#### 42.5.1.2 Molecular Identification

Matrix-assisted laser desorption-ionization time-of-flight mass spectrometry (MALDI-TOF MS) is a relatively new technology that is rapidly becoming the primary means of bacterial and yeast identification for clinical laboratories. A smear of an isolate is made on a test slide and overlaid with a low molecular weight acid solution (matrix). The prepared smear is then placed into the instrument where organism proteins (primarily) are desorbed, ionized, and vaporized under vacuum by a laser. The ionized proteins are guided toward the detector, and the time it takes for different

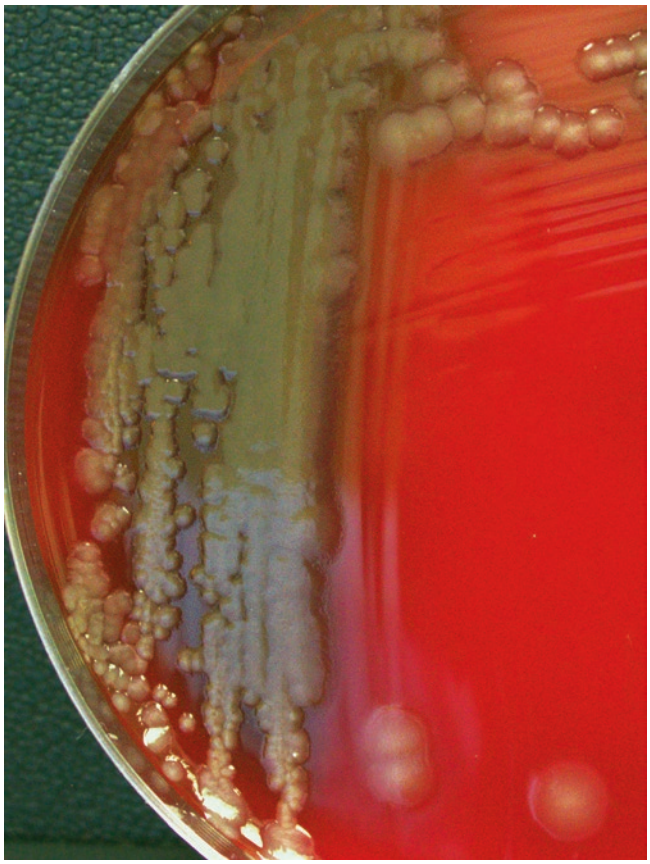

**Fig. 42.33** *Pseudomonas aeruginosa*, blood agar

molecules to reach the detector (time of flight) is measured. Lastly, the generated mass spectrum is compared to a library of known spectra to identify the isolate. The entire process takes only minutes, and the same technology can also be used to identify mycobacteria and molds.

Similar to their use in direct detection, nucleic acid probes are sometimes used to identify organisms isolated in culture, most commonly for mycobacteria and thermally dimorphic fungi. Nucleic acid sequencing is a powerful tool used by larger hospital and reference laboratories to identify isolates when other methods have failed or for organisms that cannot be identified by other means. Multiple targets for sequencing identification have been described, but the most widely applicable are 16S ribosomal DNA sequencing for bacteria and internal transcribed spacer (ITS) region sequencing for fungi.



## 42.5.2 Molds and Eukaryotic Parasites

### 42.5.2.1 Molds

The identification of molds and eukaryotic parasites is primarily accomplished by morphologic means and requires skilled, experienced laboratorians. Filamentous fungi (molds) grow as masses of hyphae (tube-like cells) called mycelia. Vegetative hyphae absorb nutrients and grow on or below the agar surface, while reproductive (aerial) hyphae project above the surface and give colonies their typical fuzzy

**Fig. 42.34** *Fusarium* and *Penicillium* colonies, Sabouraud dextrose agar

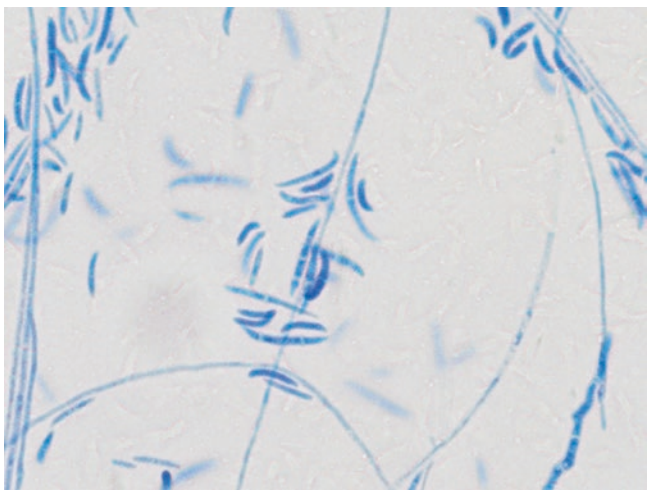

**Fig. 42.35** *Fusarium* macroconidia, lactophenol cotton blue preparation (400×)

or wooly appearance (Fig. 42.34). Observation of growth rate, pattern of growth on different media, macroscopic properties of the colony (texture, topography, coloration) along with microscopic evaluation of hyphal pigmentation and reproductive structures is usually sufficient for identification to genus (Fig. 42.35). Occasionally colonies do not produce reproductive structures in vitro necessitating identification by molecular means if the isolate is deemed clinically relevant.

### 42.5.2.2 Parasites

Traditional ova and parasite exams of stool include separate evaluations of concentrated wet mounts and permanent stained smears. The primary use of the concentrated wet mount is the detection of helminth eggs and larvae which are identified based upon egg or larval size and shape, char-

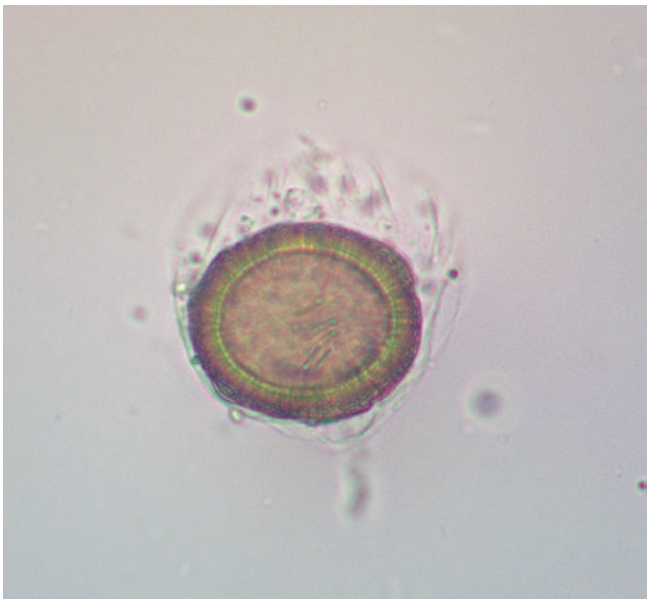

**Fig. 42.36** *Taenia* egg, wet mount (400×)

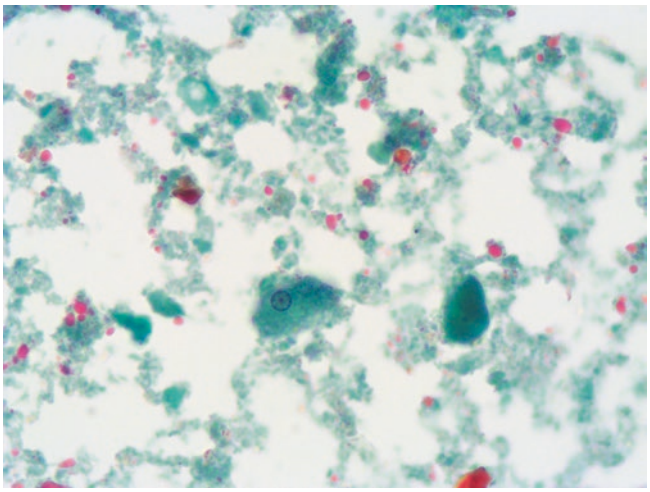

**Fig. 42.37** *Entamoeba histolytica/dispar* trophozoite, trichrome stain (1000×)

acteristics of the eggshell, and internal structures (Fig. 42.36). Protozoan cysts and coccidian oocysts may also be visualized, but identification of protozoans is usually dependent on examination of permanent stained smears, most commonly using Wheatley's trichrome. Characteristics used for protozoan speciation include organism size, number and characteristics of nuclei, consistency and components of the cytoplasm, and the presence of flagella (Fig. 42.37). The laboratory approach is similar for most other sample types (Fig. 42.38). Likewise, the differentiation of *Plasmodium* species and the identification of *Babesia* species are based on morphologic characteristics of both the parasites and infected red blood cells (Table 42.6). PCR is useful to confirm uncertain morphologic identifications and for detection of low-level infections that may be missed by other means. An estimate of the blood parasite burden (parasitemia), expressed as either the percentage of infected

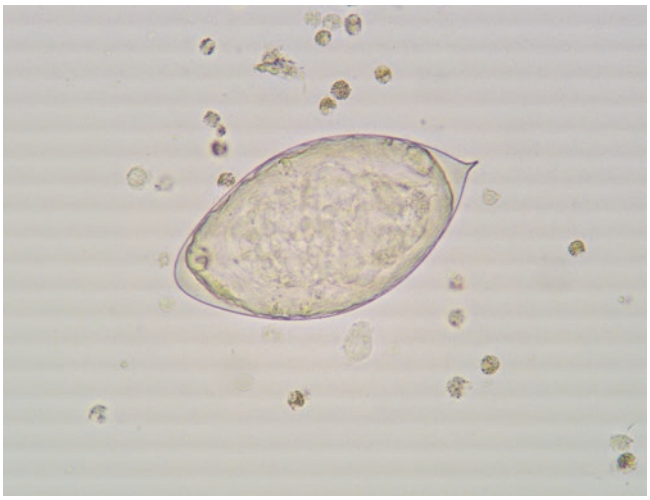

**Fig. 42.38** *Schistosoma haematobium* egg, urine sediment (200×)

red blood cells or number of parasites per microliter, is determined for all positive samples to monitor response to therapy. Characteristics for the speciation of microfilaria include the presence or absence of a sheath and distribution of nuclei.

### 42.5.3 Viruses

Although it is not possible to directly see viruses using light microscopy, the morphological effects they have on the host cells can be. These virus-induced host cell changes, collectively termed cytopathic effect (CPE), include rounding, swelling, clumping, granulation, increased refractility, vacuolation, nuclear condensation, syncytia, and lysis (Figs. 42.39 and 42.40). Some viruses, notably influenza and parainfluenza viruses, do not always produce readily apparent CPE, so the technique of hemadsorption is used to detect their presence. Hemadsorption takes advantage of the fact that cells infected with influenza and parainfluenza viruses express hemagglutinins. A suspension of guinea pig red blood cells is added to the monolayer which is then briefly refrigerated. The observation of red blood cells adhering to the monolayer constitutes a positive hemadsorption screen (Fig. 42.41). Combining the specimen source, pattern of CPE (or hemadsorption), rate of CPE formation, and the cell lines affected usually allows provisional identification. For definitive identification, a suspension of the monolayer cells is fixed to glass microscope slides and stained with fluorescent-labeled virus-specific antibody. Lastly, the stained smears are evaluated for cytoplasmic or nuclear fluorescence, indicating the specific virus present (Fig. 42.42).

Shell vial monolayers are also stained and examined for viral antigens but prior to the development of CPE. This technique is faster than traditional culture primarily since the antibodies used for staining are specific for antigens expressed early in the viral life cycle. Shell vials are also used to culture the obligate intracellular bacterium *Chlamydia trachomatis*.

**Table 42.6** Primary morphologic characteristics of *Plasmodium* and *Babesia* in thin blood films

| Organism | Infected RBC Size/Morphology | Multiply infected RBCs | Trophozoite morphology | Stages in peripheral blood |
|---|---|---|---|---|
| *P. vivax* | Normal to enlarged<br>Schüffner's dots/stippling | Occasional | Rings[a] ≥1/3 RBC diameter<br>Amoeboid when mature | All |
| *P. falciparum* | Normal<br>Maurer's clefts (occasional) | Common | Delicate rings <1/3 RBC diameter<br>Double chromatin dots<br>Appliqué forms | Rings<br>Gametocytes |
| *P. ovale* | Normal to enlarged; frequently oval; may be fimbriated<br>Schüffner's dots/stippling | Occasional | Rings ≥1/3 RBC diameter<br>Compact when mature | All |
| *P. malariae* | Normal to small | Rare | Rings <1/3 RBC diameter<br>Compact when mature; band and basket forms | All |
| *P. knowlesi* | Normal<br>May have stippling with late trophozoites | Common | Rings <1/3 RBC diameter; resemble *P. falciparum*<br>Double chromatin dots<br>Appliqué forms (rare)<br>May resemble *P. malariae* when mature | All |
| *Babesia* spp. | Normal | Common | Delicate rings <1/3 RBC diameter; variable size and shape<br>Extracellular forms common<br>Tetrad forms (rare) | Rings |

[a]Rings (ring forms) = early trophozoites

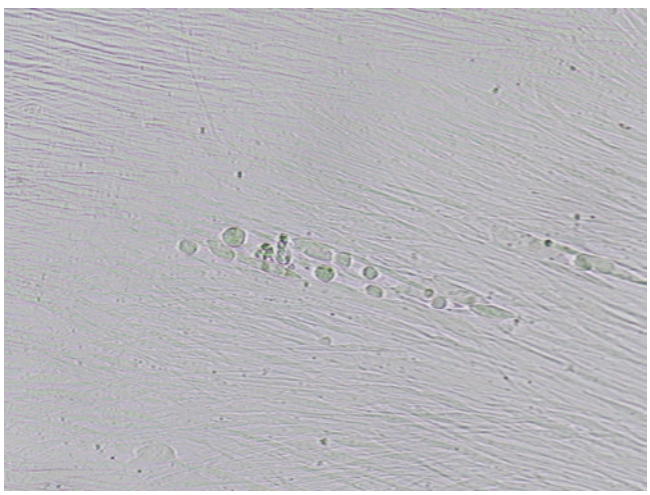

**Fig. 42.39** Cytomegalovirus CPE, human diploid fibroblasts (100×)

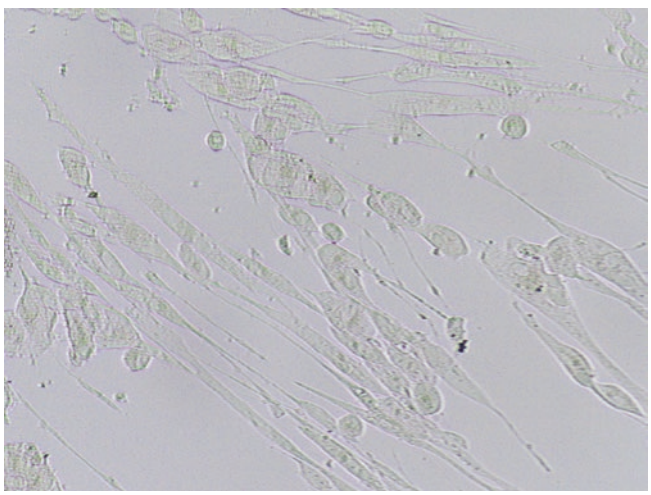

**Fig. 42.40** Herpes simplex virus CPE, human diploid fibroblasts (100×)



## 42.6 Antimicrobial Susceptibility Testing

### 42.6.1 Bacteria

#### 42.6.1.1 Aerobic and Facultative Bacteria

In vitro antimicrobial susceptibility testing is one of the most important and directly useful activities of clinical microbiology laboratories. There are, however, some limitations that must be considered when using the results for patient management. In vitro test results do not account for drug or patient variables such as serum protein binding and inactivation, conditions at the site of infection (e.g., pH), drug interactions, immune deficiency, organism burden, polymicrobial infections, or the replication state of the offending organisms (actively replicating vs. dormant). Laboratory testing exposes isolates to serum-achievable drug concentrations and therefore may not accurately reflect activity in body sites where the drug is concentrated (e.g., the bladder)

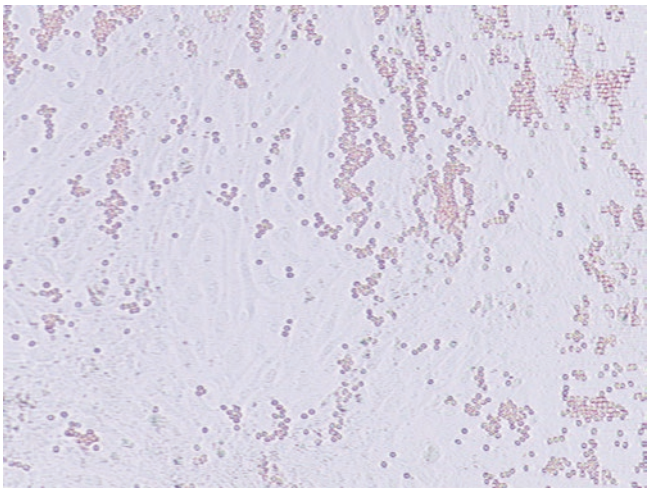

**Fig. 42.41** Positive hemadsorption test, primary monkey kidney (100×)

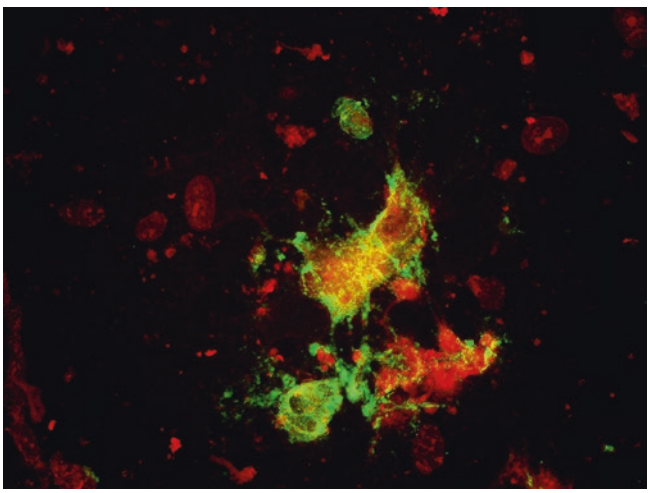

**Fig. 42.42** Parainfluenza 2 culture confirmation, immunofluorescence (400×)

or excluded (e.g., the central nervous system). Additionally, standardized methods do not exist for all antimicrobial agents or potentially significant organisms. For these reasons, in vitro susceptibility testing should be considered as a guide for therapy, not a guarantee of efficacy.

Susceptibility testing is only performed using pure isolates, and results are not reported until an isolate has been identified. These two conditions for testing and reporting may delay the availability of results, particularly the need for pure isolates. Many primary cultures contain multiple colony types, and subculture may be required since testing mixed populations can lead to erroneous results.

In general, susceptibility testing is normally performed for bacteria with the characteristics outlined in ▶ Box 42.3. The selection of antimicrobial agents for routine testing and reporting is based upon input from clinical staff, hospital pharmacists, and laboratory experts. The specimen source must also be considered as some antimicrobial agents only reach effective concentrations in certain anatomic locations. For example, the results of cefazolin susceptibility testing are quite useful to guide therapy for a urinary tract infection caused by *E. coli* since the antibiotic reaches high concentrations in the urine. In contrast, the results of cefazolin susceptibility testing for an *E. coli* isolate cultured from cerebrospinal fluid would be irrelevant since the antibiotic does not adequately penetrate the blood-brain barrier, and should never be used to treat meningitis. Agents to which organisms are intrinsically resistant are not tested, and agents that don't reach adequate concentrations in the infected site, if tested, are not reported.

**Box 42.3 General Characteristics of Bacterial Isolates Routinely Selected for Antimicrobial Susceptibility Testing**

- Rapidly growing, non-fastidious
- Known to have variable susceptibility profiles
- Established pathogens
- Isolated in predominant quantity or from normally sterile sites
- Standardized methods for testing and interpretation are available

Although isolates are regularly tested against multiple antimicrobial agents, most laboratories release the results selectively. The basic premise of selective (conditional) antimicrobial reporting is to report the least toxic and narrowest-spectrum agents when they are susceptible; broader-spectrum agents are only reported when the narrow-spectrum agents are non-susceptible or less clinically appropriate. The practice of selective reporting supports antimicrobial stewardship efforts and should encourage dialogue between the laboratory and the care provider.

For accuracy and reproducibility, the procedures used for in vitro antimicrobial susceptibility testing must be rigidly standardized including the test isolate inoculum, growth medium, incubation conditions, and the concentration of antimicrobial agents used. The inoculum is a suspension of the test isolate prepared to match a turbidity standard equivalent to approximately $10^8$ colony-forming units (CFU)/mL. Bacterial susceptibility is most often performed using Mueller-Hinton broth and agar, which are defined media that support the growth of most aerobes and facultative anaerobes. These media may be modified by the addition of supplemental growth factors to allow testing of more fastidious organisms including streptococci and *Neisseria meningitidis*. Incubation is usually performed in ambient air at 35 °C, but added $CO_2$ is required for some organisms. The duration of incubation is typically 16–18 h but may be shorter or longer depending on the organism/drug combination and antimicrobial susceptibility method used. Susceptibility test results are interpreted as susceptible, intermediate, or resistant (▶ Box 42.4) using published guidelines. Many laboratories also perform rapid immunochromatographic or latex agglutination assays for methicillin (oxacillin) resistance in isolates of *Staphylococcus aureus* (Fig. 42.43). These tests detect expression of the altered penicillin-binding protein

**Box 42.4 Antimicrobial Susceptibility Test Interpretations[a]**

**Susceptible**
- Isolate is inhibited by serum-achievable drug concentrations
- Drug is likely to be effective clinically
- Susceptible-dose dependent: The susceptibility of an isolate depends on optimized drug dosing

**Intermediate**
- Isolate is inhibited by concentrations of a drug that approach but do not reach usually achievable serum concentrations
- Implies clinical efficacy in body sites where the drug is concentrated or when higher doses can be used

**Resistant**
- Isolate is not inhibited by serum-achievable drug concentrations
- Unlikely to be effective clinically

[a]Other interpretive categories exist for some organism/drug combinations

encoded by *mec*A and provide results 1 day sooner than growth-dependent methods.

The antimicrobial susceptibility tests most often used in clinical laboratories fall into two general categories: dilution and diffusion. Classical broth macrodilution (tube dilution) employs serial doubling dilutions of each antimicrobial agent in Mueller-Hinton broth to create a range of antibiotic concentrations. An aliquot of the standardized bacterial suspension is added to each dilution including an antibiotic-free growth control tube. After incubation, the tubes are examined for growth by assessing the turbidity of the fluid. The minimum inhibitory concentration (MIC) is reported as the lowest concentration of an antimicrobial agent that inhibits visible growth. Broth microdilution is analogous to broth macrodilution except the volumes of both the dilutions and inoculum used are much smaller. Clinical laboratories generally employ prepared broth microdilution panels available commercially as stand-alone products or as components of automated identification and susceptibility systems. Commercial systems utilize either reference broth microdilution or modifications based on the method.

As with dilution methods, there are two principle types of diffusion susceptibility tests. Disk diffusion utilizes paper disks containing specific concentrations of an antimicrobial agent. To perform the test, the standardized suspension is distributed evenly onto a Mueller-Hinton agar plate so that after incubation a continuous "lawn" of growth will occur wherever the organism is not inhibited by an antimicrobial. The disks are applied to the inoculated plate, and the antimicrobials diffuse into the agar and away from the disk, forming a concentration gradient. After incubation, the plates are examined for clear areas present around the disks where the organism failed to grow. These areas are referred to as zones of inhibition. Bacterial growth is visible around the disks only in the areas where the concentration of the drug is not

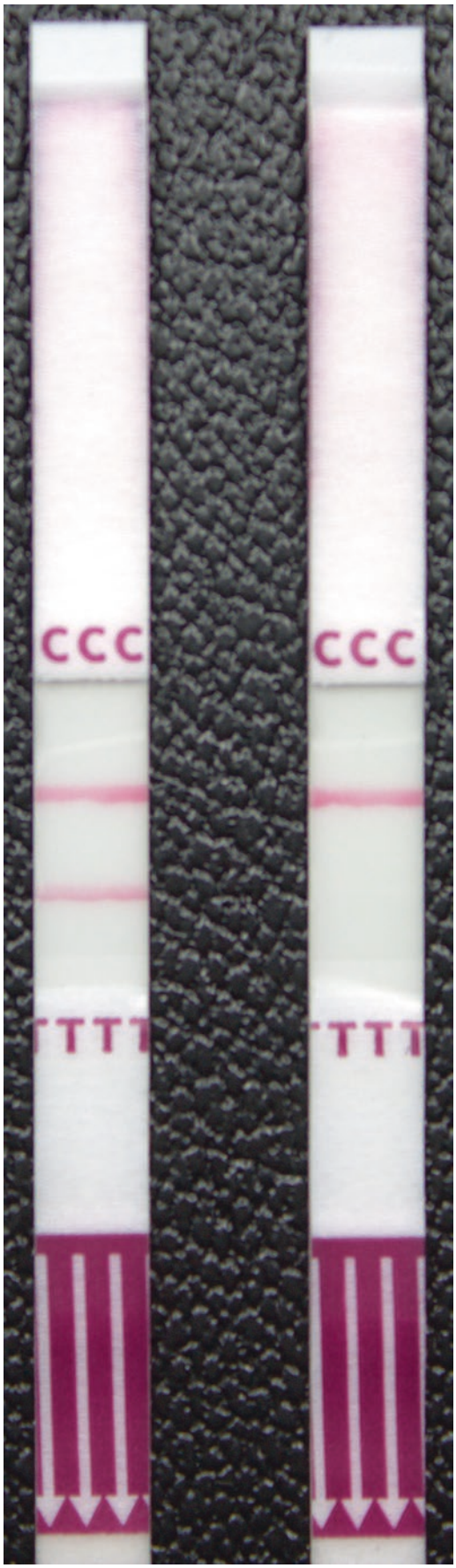


**Fig. 42.43** Penicillin-binding protein assay, immunochromatography

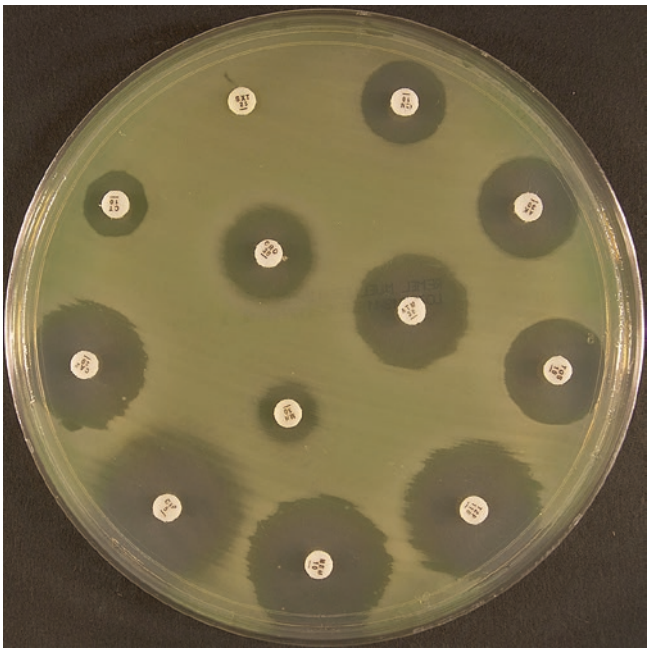

**Fig. 42.44** Disk diffusion, *Pseudomonas aeruginosa*

sufficient to exert an inhibitory effect (Fig. 42.44). The diameters of the zones of inhibition are measured in millimeters and compared to standardized interpretive criteria to determine susceptibility. Because diffusion depends upon the molecular weight and solubility of the antimicrobial tested, zone sizes corresponding to susceptible, intermediate, and resistant are unique to each organism or organism group and each antimicrobial agent tested.

Gradient diffusion is performed much like disk diffusion but uses plastic strips instead of paper disks. The strips have a dried continuous antimicrobial concentration gradient on one side and a corresponding scale on the other (Fig. 42.45). Agar plates are prepared as for disk diffusion, and the strips are laid onto the prepared surface. Once applied, a continuous and exponential gradient of antimicrobial concentrations is formed around the strip. Elliptical zones of inhibition are formed after incubation, and the MIC is read from the scale where the ellipse intersects the strip.

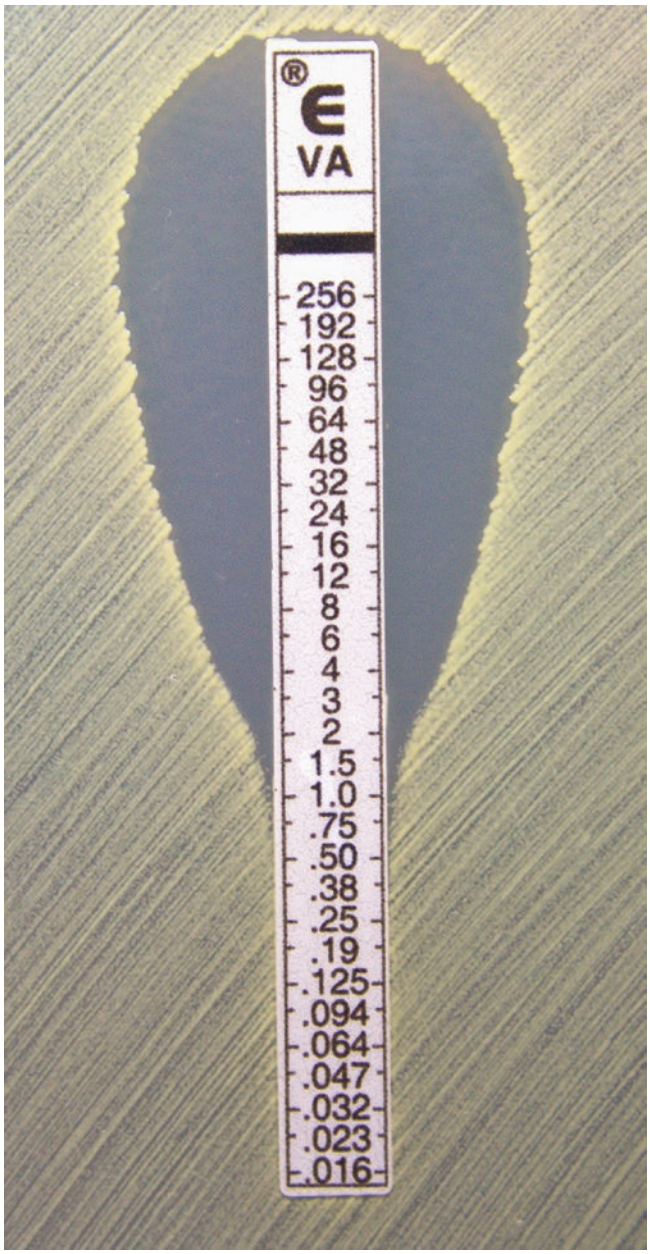


**Fig. 42.45** Gradient diffusion, *Staphylococcus aureus*

### 42.6.1.2 Anaerobic Bacteria

Due to the comparatively long turnaround time for results and the general efficacy of empiric therapy, many clinical laboratories do not perform susceptibility testing for anaerobes and would refer isolates to an outside laboratory when requested. Beta-lactamase testing is rapid, available in most laboratories, and should be considered for anaerobes other than members of the *Bacteroides fragilis* group, which are presumed to be beta-lactamase positive. More extensive testing should be considered for isolates of *Bacteroides*, *Fusobacterium*, *Prevotella*, and *Clostridium* species, especially when isolated from normally sterile sites, when prolonged treatment is required or if treatment failure is suspected. Available methods to determine antibiotic susceptibility in anaerobic bacteria include agar dilution, broth dilution, and gradient diffusion.

### 42.6.1.3 Mycobacteria

Susceptibility testing of mycobacteria is primarily performed by larger academic medical centers, reference laboratories, and public health departments. Testing is especially important for members of the *Mycobacterium tuberculosis* complex (MTBC) and should be performed for all initial isolates and when there is either clinical evidence of failure or the patient remains culture positive after 3 months of therapy.

Antimicrobial susceptibility testing for MTBC is performed using the proportion method. Agar proportion employs solid media containing a single specific concentration of each antimicrobial. A standardized suspension of the isolate is prepared, and measured aliquots of this suspension are deposited onto agar plates that have been prepared both with and without (growth control) each of the antimicrobials

of interest. Once sufficient growth occurs, the number of colonies on each drug-containing plate is compared to the number on the growth control. Isolates are considered susceptible to an agent if the number of colonies on the drug-containing plates is ≤1% of the number seen on the growth control plate. A modified proportion method using liquid media can be performed by some automated mycobacterial culture systems and is interpreted in a similar manner. Broth microdilution is used when testing nontuberculous mycobacteria.

#### 42.6.1.4 Fungi

Antimicrobial susceptibility testing of yeasts, especially *Candida* species isolated from sterile sites, has become routine in many laboratories. Broth microdilution is the most widely available method, but applications also exist for disk and gradient diffusion. Susceptibility testing of molds is primarily performed by specialty and reference laboratories using broth dilution. The duration of incubation for fungal susceptibility testing depends on the organism/drug combination and ranges between 1 and 10 days.

#### 42.6.1.5 Nucleic Acid Tests

Molecular methods for the detection of genetic resistance markers in clinical specimens and positive blood cultures are increasingly available, either as stand-alone tests or as part of multiplexed nucleic acid amplification panels. Assays for the detection of *mec*A and *van*A/*van*B (vancomycin resistance in enterococci) directly in select clinical specimens are in widespread use. Detection of *rpo*B mutations resulting in rifampin resistance has also become a routine component of MTBC testing, either directly in clinical specimens or from positive cultures. Broader use of NAAT to predict susceptibility can be hampered by the number of potential mutations that must be detected. Nucleic acid sequencing has many applications and is used by specialty and referral laboratories to detect resistance determinants in a wide range of microorganisms.

## Further Reading

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# Supplementary Information




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# Answers to the Chapter Exercises

## Chapter 1

1. *Staphylococcus aureus*, methicillin resistant or MRSA
2. *Mycobacterium marinum*
3. *Aeromonas hydrophilia, Vibrio vulnificus*
4. False
5. True
6. False
7. True
8. True

## Chapter 2

1. E
2. C
3. A
4. G
5. B
6. H
7. D
8. F

## Chapter 3

1. B. Provide supportive care
2. C. *St*aphylococcus aureus
3. B. Epstein Barr specific anti-IgM against viral capsid antigen
4. A. Bartonella henselae
5. D. Redness, swelling, heat, and pain

## Chapter 4

**Matching:**

Answer Key: 1E, 2D, 3E, 4F, 5A

## Chapter 5

1. a. This patient scores 1 using the Centor criteria: age 15–44 years (0 point), no fevers (0 point), absence of tender cervical lymphadenopathy (0 point), cough (0 point), and tonsillar exudates (1 point). Under the current recommendations, no further diagnostic evaluation is needed, and no antibiotics are warranted since there is a low likelihood of GAS infection. Answer D would be appropriate for patients with 2 or more points. Empiric treatment with antibiotics is no longer recommended.

2. c. It is important to differentiate between critical and stable patients. This patient presents with several concerning features including respiratory difficulty, positioning, and drooling. Suspicion for airway compromise secondary to an infection of the oropharynx, retropharynx, or epiglottis should be high. In critical patients, the ABCs are always first line of treatment: A for airway, B for breathing, and C for circulation. *Everything else* waits until the patient has been stabilized. Although a CT scan would likely be a very appropriate test in a patient like this, sending a critical patient to the CT scanner, which often does not have the same resources as an emergency department or intensive care unit, places the patient at serious risk should they decompensate en route. Many patients with serious infections of the pharynx, parapharyngeal spaces, or epiglottis would also not tolerate lying flat.

3. c. Oral candidiasis typically does not affect healthy adults, so an immunocompromising condition should be suspected in this patient. Her history of intravenous drug use puts her at higher risk of contracting several blood-borne illnesses, including HIV. HIV testing is appropriate in the management of this patient. Antibiotics are not indicated for the treatment of candidiasis. Thrush is a clinical diagnosis that does not need laboratory culture confirmation.

4. a, b, c. The management of small, minimally symptomatic peritonsillar and other deep neck space abscesses is evolving and remains somewhat controversial. No single approach to treatment has proven to be superior to any other. Many of these cases will resolve with antibiotic treatment and supportive care; however some ultimately will require drainage. In making the decision about how to manage such patients, the provider must weigh the risks of performing a procedure versus the risks of not draining a potential abscess. The only choice listed that would not be appropriate for this patient would be to take her to the operating room for incision and drainage under general anesthesia because her symptoms are mild and the collection is small.

## Chapter 6

1. *Bordetella pertussis*
2. False – pertussis occurs in *all* age groups.
3. Young infant population under 4 months of age.
4. The clinical definition of pertussis disease is a cough greater than or equal to 14 days and one or more of the following symptoms: paroxysmal cough, inspiratory whoop, or post-tussive vomiting.
5. False – Neither natural pertussis infection nor immunization produces lifelong immunity. Repeated vaccination with pertussis-containing vaccines is needed to protect a person against pertussis.
6. True – The disease consists of three stages: The catarrhal stage which may last as long as 10 to 14 days, the paroxysmal stage which may last as long as 42 days, and the convalescent stage which may last for as long as 56 days.
7. True
8. Test of choice for diagnosis in all age groups is pertussis real-time polymerase chain reaction (PCR) assays. The most reliable results are obtained within the first 3 to 4 weeks of the cough illness.
9. The antibiotics that are effective in the treatment or chemoprophylaxis of pertussis are the azalides (azithromycin), macrolides (erythromycin, clarithromycin), and trimethoprim-sulfamethoxazole (TMP-SMX).
10. True

## Chapter 7

**Matching:**

Answer Key: 1C, 2B, 3A, 4E, 5D

**Multiple choice:**

B is the best answer. Mist is not indicated as there is no demonstrated clinical benefit. Croup is caused by viruses, so antibiotics are not indicated. If a child is found to have croup due to influenza virus, treatment with the antiviral medication, oseltamivir, can be considered.

**Practical Examples:**

D. Bronchiolitis. This is the best answer for this clinical scenario. The child presents with classic bronchiolitis including a prodrome with upper respiratory symptoms followed by the onset of tachypnea and retractions. He is mildly hypoxemic in room air and has prominent nasal flaring with intercostal retractions and wheezing. A. Respiratory syncytial virus, this is the most common viral pathogen causing bronchiolitis worldwide. D. Management of bronchiolitis is generally supportive with the provision of oxygen as needed and fluids. A trial of albuterol can be considered since a subset of infants and young children may benefit, although evidence does not support its routine use.

## Chapter 8

**Matching:**

Answer Key: 1I, 2F, 3G, 4J, 5A, 6H, 7B, 8D, 9C, 10E

## Chapter 9

1.
2.
3.

## Chapter 10

1. A
2. B

## Chapter 11

**Matching:**

Answer Key: 1d, 2b, 3f, 4a, 5h, 6g, 7c, 8e

1. c
2. a—Late gadolinium enhancement in a patchy sub-epicardial pattern is consistent with myocarditis
3. c

## Chapter 12

1. A
2. A
3. A
4. True
5. False

## Chapter 13

1. C
2. A
3. D
4. B
5. C

## Chapter 14

1. C. *Klebsiella pneumoniae*
2. B. Use of transcatheter arterial embolization procedures
3. C. Including intravitreal antibiotics in the treatment regimen
4. A. Percutaneous drainage

## Chapter 15

**Matching:**

Answer Key: 1E, 2D, 3A, 4B, 5C

**Case 1:**

C

**Case 2:**

A

**Case 3:**

D

**Case 4a:**

C

**Case 4b:**

B

## Chapter 16

1. b
2. d
3. b
4. a
5. d

## Chapter 17

1. c
2. a
3. False
4. a, b, d

## Chapter 18

1. b
2. e
3. b

## Chapter 19

1. A-iv; B-vi; C-ii; D-i; E-v; F-iii
2. D
3. C
4. B
5. E

## Chapter 20

1. 1G; 2E; 3B; 4A,D; 5F; 6D; 7C,D,E,F,G

2. D

3. 1D,F; 2E; 3B; 4C

4. C

## Chapter 21

1. B. Guillan Barré syndrome

2. D. Spasticity. If Spasticity develops, it is a late (and not acute/early) manifestation of acute transverse myelitis.

3. D. Unknown. Although many of the AFM cases were preceded by mild respiratory illness due to EV-D68, extensive testing has not identified EV-D68 or other pathogens in the CSF. Despite the strong association, causality remains in doubt.

## Chapter 22

1. A 17-year-old girl presents with a diffuse headache and photophobia. The onset has been gradual over the last few days, but is getting worse.

   - *What additional information would you like to obtain?*

A thorough history can help direct diagnostic testing. Symptoms such as fever, recent illness, location of the headache, palliative and provocative factors, and associated symptoms should be asked. These factors can direct a differential diagnosis for headache, and if needed, for infectious causes of headache.

Social history should be obtained. Elements include history of sexual activity, new sexual partners, new living environment (such as a dormitory or barracks), outdoor exposures to mosquitoes and ticks, travel history, and ill contacts.

A complete review of systems can help uncover associated symptoms which may be important in diagnosing the patient.

A careful physical examination should be performed, including evaluating for signs of meningismus and looking for characteristic rashes.

- *What laboratory studies would you like to obtain?*

A complete blood count with differential can be helpful. If an invasive procedure is planned, a coagulation screen can be obtained.

Other blood studies that may be helpful include blood cultures.

A lumbar puncture to obtain cerebrospinal fluid will help determine if her illness is meningitis or not.

- *What is included in your differential diagnosis? How does this change if the patient is 3 months old? How would this change if the patient is 70 years old taking anticoagulation due to a history of atrial fibrillation?*

The differential diagnosis for headache can be broad. Bacterial meningitis and aseptic meningitis are considerations. Migraine headache is also a consideration. Sinusitis may cause headache, but may not cause photophobia. Also, intracranial processes such as venous sinus thrombosis can lead to headache. There are numerous other causes for headache in the adolescent girl—the list provided is not exhaustive.

A 3-month-old infant would not be able to verbalize the presence of a headache. Instead, she may present as a fussy or intractably crying infant. Colic is a non-life threatening condition which includes prolonged crying. Other, more serious problems should be evaluated—including the possibility of meningitis, otitis, or other serious infections. Noninfectious causes of irritability in the infant can include corneal abrasions, intussusception, testicular torsion, and hair tourniquets around fingers, toes, or genitals. Again, this is not an exhaustive list of potential causes of irritability in the infant, but history and a careful examination can lead to a diagnosis.

The elderly adult has a different set of risk factors, including vascular disease and bleeding risk. Other risks may be identified on review of medical history. For the patient on anticoagulation, hemorrhagic stroke or ruptured intracranial aneurysm should be considered.

2. A lumbar puncture is performed. Initial results are below:

   - Nucleated cell count: 15 cells/mm$^3$, 75% lymphocytes, 25% neutrophils. The CSF is described as clear, with no red blood cells noted.
   - Total protein 55 g/dl, glucose 60 g/dl
     - *Which diagnosis is more likely with these lab results? How would this be different if the patient were 3 weeks old? 6 weeks old?*

For the 17-year-old, this is consistent with pleocytosis and suggests meningitis. The nucleated cell count differential suggests a viral etiology.

For the 3-week-old infant, these values fall within normal limits. However, if the child was 6 weeks old (just 3 weeks older!), the findings would be concerning for a meningitis.

- *How would your differential diagnosis change if the patient was a recent immigrant to the United States, and the cell count showed 115 cells/mm$^3$, with 90% monocytes?*

This child has a different epidemiologic risk profile than if the patient had never traveled. Additionally, since the differential has a monocytic predominance, there should be consideration of other pathogens. These include tuberculosis and fungi.

3. A Gram stain shows no organisms. Bacterial cultures reveal no growth.

   - *What additional tests would help diagnose the 17-year-old girl?*

Polymerase chain reaction could be ordered to diagnose enterovirus and herpes simplex virus, two of the most common causes of aseptic meningitis. Other tests, such as HIV testing, could reveal an underlying cause for other illnesses, such as Cryptococcus meningitis or HIV-related aseptic meningitis.

- *What tests would you order if the patient were an infant?*

Infants are at risk for herpes simplex virus infection in the first weeks of life. They can also be prone to other viral infections like enterovirus and parechovirus. A review of the delivery record including maternal labs can direct diagnostic testing, which may include PCR against specific pathogens.

- *What tests would you order if the patient spent time outdoors and reported mosquito or tick bites?*

With this epidemiologic exposure, consideration should be given to West Nile and other arboviruses, as well as Lyme and other tick-borne illness. West Nile and arboviruses are primarily diagnosed with antibody assays on CSF or serum. Lyme may be diagnosed with an antibody assay confirmed by Western blot. Lyme may also be diagnosed with PCR on the CSF, although a negative PCR does not exclude Lyme disease.

- *What additional considerations would you have if the patient was infected with HIV?*

Depending on the degree of immunosuppression, patients with HIV could be at risk for many infections. HIV itself can cause an aseptic meningitis, particularly during acute conversion. Hosts with HIV and low CD4 cell counts are at risk for Cryptococcus meningitis, JC virus, and central nervous system toxoplasmosis. Patients with AIDS are also at risk for CMV reactivation disease.

## Chapter 23

### Case 1

1. C
2. A-D
3. B (if black-and-white image, both A or B could be correct.)
4. B

### Case 2

5. D
6. C

### Case 3

7. A
8. B (if black-and-white image, A or B could be correct.)
9. D

## Chapter 24

1. Headache
2. Age (newborns)
3. In the vertebral bodies (vertebral osteomyelitis)
4. *S. aureus*
5. The frontal sinuses

## Chapter 25

1. c
2. Measles, mumps, varicella, rotavirus, influenza, polio, rabies
3. 1D, 2E, 3A, 4B, 5C

# Chapter 26

## Tetanus

1. Identify the different risk factors associated in the transmission and exposure to tetanus infection.

**Answer.** Table 26.1 lists the various ways tetanus infection gets into your body and clinical history increasing index of suspicion for tetanus which includes burns, crush injuries, injuries with dead tissues, intravenous drug use, minor surgical procedures or rectal/vaginal instrumentation, puncture wounds from a nail or recent needle injection, and wounds contaminated with feces, dirt, saliva.

2. Name the various symptoms and clinical presentation of tetanus.

**Answer.** Table 26.2 lists the various signs and symptoms associated with tetanus which includes difficulty swallowing, fever and sweating, headache, jaw cramping, labile blood pressure and tachycardia, painful muscle stiffness of the body, and sudden involuntary muscle tightening or muscle spasms.

Table 26.3 enumerates the overlapping clinical forms of tetanus which includes cephalic tetanus, generalized tetanus, localized tetanus, and neonatal tetanus.

3. Ask the director of the Microbiology Lab if they have photo micrographs on file of the *C. tetani* bacteria showing its characteristic terminal spore. The Centers for Disease Control and Prevention's website has a repository of pictures depicting the terminal spore of *C. tetani*.

**Answer.** Learning experience may vary with local microbiology unit.

4. Describe the overlapping clinical forms of tetanus and list the differential diagnoses for tetanus.

**Answer.** Table 26.3 enumerates the overlapping clinical forms of tetanus which includes cephalic tetanus, generalized tetanus, localized tetanus, and neonatal tetanus.

Tetanus is a clinical diagnosis; however, there are several differential diagnoses that need to be ruled out which includes adverse drug reactions (phenothiazine reaction, strychnine poisoning), hypocalcemic tetany, meningitis, encephalitis, seizures, rabies, and conversion disorder.

5. Discuss the cornerstone of management and complications of patients with tetanus.

**Answer.** Tetanus is a medical emergency requiring hospital admission. Eradication of *C. tetani*, neutralization of tetanus toxins, and supportive care remain the cornerstone in the management and care of patients with tetanus.

## Diphtheria

1. Describe the pseudomembrane and the "Bull neck" signs associated with the clinical presentation of diphtheria.

**Answer.** Pseudomembrane is a local inflammatory reaction induced by bacteria that is dense and adherent in the superficial layer of the skin or respiratory mucosa due to diphtheria toxin that triggers the production of a necrotic, coagulated mass of fibrin, leukocytes, dead respiratory epithelial cells and bacteria.

"Bull neck" is a sign of severe disease associated with diphtheria due to extensive neck swelling with cervical lymphadenitis.

2. Identify the different end organs affected by the diphtheria toxin.

**Answer.** Table 26.6 lists the different clinical forms of diphtheria which identify the different end organs initially affected by the diphtheria toxin as follows, respiratory diphtheria (nasal, laryngeal, pharyngeal, and tonsillar) and cutaneous diphtheria.

3. Correspond with the Microbiology Laboratory regarding which appropriate specimens to collect from patients with a clinical diagnosis of diphtheria.

**Answer.** Learning experience may vary with local microbiology unit.

A swab specimen from beneath the pseudomembrane is the most valuable specimen, but positive results can also be obtained from nasopharyngeal swab samples. Direct examination of swab samples using a Gram stain (Fig. 26.8) has limited utility, but swab samples can be analyzed with Neisser or Loeffler methylene blue stains with positive samples demonstrating metachromatic granules. For optimum visualization of these characteristic granules, the bacterium should be grown on Loeffler culture medium before staining. PCR-based direct specimen detection systems for the diphtheria tox gene have been described.

4. Describe the different clinical forms of diphtheria and list the differential diagnosis of diphtheria.

**Answer.** Table 26.6 lists the different clinical forms of diphtheria which includes respiratory diphtheria (nasal, laryngeal, pharyngeal, and tonsillar) and cutaneous diphtheria.

There are other disease processes that may be associated with membranous pharyngitis, and ◘ Table 26.9 lists the differential diagnosis which includes other microbiologic agents (*Arcanobacterium hemolyticum, Borellia vincenti*) associated with Vincent's angina or necrotizing gingivitis, *Candida albicans, Haemophilus influenza associated with epiglottitis, Staphylococcus aureus, Streptococcus pyogenes* (Group A Streptococcus), *Toxoplasma spp.,* viruses (adenovirus, infectious mononucleosis due to EBV, herpes simplex virus) as well as use of medications like antineoplastic agents like methotrexate that may cause formation of pharyngeal membrane and long-term use of corticosteroid (e.g., prednisolone) may cause oral thrush.

5. Discuss the cornerstone of management and complications of patients with the clinical diagnosis of diphtheria.

**Answer.** Antitoxin and antimicrobial regimen remains the cornerstone in the care and management of patients with provisional clinical diagnosis of diphtheria.

Respiratory diphtheria may progress to severe and life-threatening complications as listed in ◘ Table 26.8 which includes cranial and peripheral neuropathies, myocarditis with associated heart block, renal Insufficiency, toxic circulatory collapse, and upper airway obstruction due to extensive membrane formation or cervical edema (Bull-neck). Some patients with pharyngeal diphtheria may have nasal speech due to palatal palsy.

## Botulism

1. Identify the different risk factors associated with the development of botulism.

**Answer.** ◘ Table 26.13 lists the different kinds of botulism and the different factors associated with their development. *Foodborne botulism* occurs after eating foods (improperly canned, fermented, or preserved homemade foods) contaminated with botulinum toxin. *Infant botulism* occurs if spores of the bacteria get into the infant's intestine, germinate, and produce botulinum toxin. *Wound botulism* occurs if spores of the bacteria get into the wound (after traumatic injury, surgery, or intravenous drug use), germinate, and produce botulinum toxin. *Adult intestinal toxemia* is a rare kind of botulism due to spores of the microorganism getting into adult's intestine, germinate, and produce toxin similar to infant botulism. Those with medical conditions involving the digestive tract may be at risk. *Iatrogenic botulism* occurs if excessive botulinum toxin is injected for cosmetic reasons (for wrinkles) or medical reasons (for migraine headaches).

2. Differentiate the various symptoms and clinical presentation of classic botulism versus infant botulism.

**Answer.** ◘ Table 26.15 lists the various clinical presentations of classic botulism and infant botulism.

*Classic botulism* may present with blurred vision, diplopia (double vision), drooping eyelids, dry mouth, dysarthria (slurred or slow speech), dysphagia (difficulty swallowing), dysphonia (hoarse voice), muscle weakness, if not treated may progress to descending paralysis involving respiratory muscles, arms, and legs.

*Infant botulism* may present with lethargy, constipation, feed poorly, poor muscle tone, or with weak cry.

3. Correspond with the Microbiology Laboratory regarding which culture and bioassays are available locally and which appropriate specimens to collect from patients with a clinical suspicion for botulism.

**Answer.** Learning experience may vary with local microbiology unit.

Most hospital laboratories are not properly equipped to process specimens from patients suspected of having botulism. Before collecting any specimens the medical care provider should call their state health department's or CDC's emergency 24-h telephone number (770-488-7100) so that appropriate action can be taken to establish the diagnosis, initiate therapy, and investigate the case. Laboratory confirmation of foodborne botulism is the detection of botulinum toxin in serum, stool, or patient's food, or the isolation of *Clostridium botulinum* from stool. This case definition is also used for adult and child non-foodborne cases. For wound botulism, laboratory confirmation entails detection of botulinum toxin in serum, or isolation of *Clostridium botulinum* from the wound. Bioassays for botulinum toxin are currently the most important laboratory tests for diagnosis of botulism. Currently, the only reliable assay is the mouse bioassay together with neutralization of mouse toxicity with type-specific antitoxins.

◘ Table 26.16 summarizes the list of specimens for diagnostic assay in cases of botulism.

4. Describe the different clinical forms of botulism.

**Answer.** ◘ Table 26.13 lists the different clinical forms of botulism. *Foodborne botulism* occurs after eating foods (improperly canned, fermented, or preserved homemade foods) contaminated with botulinum toxin. *Infant botulism* occurs if spores of the bacteria get into the infant's intestine, germinate, and produce botulinum toxin. *Wound botulism* occurs if spores of the bacteria get into the wound (after traumatic injury, surgery, or intravenous drug use), germinate, and produce botulinum toxin. *Adult intestinal toxemia* is a rare kind of botulism due to spores of the microorganism getting into adult's intestine, germinate, and produce toxin similar to infant botulism. Those with medical conditions

involving the digestive tract may be at risk. *Iatrogenic botulism* occurs if excessive botulinum toxin is injected for cosmetic reasons (for wrinkles) or medical reasons (for migraine headaches).

5. Discuss the different treatment regimens in managing patients with botulism as well as the associated complications.

**Answer.** Botulism is a medical emergency and any patients with clinical suspicion for botulism should be managed urgently with antitoxin. Laboratory confirmation of the diagnosis for botulisms should not preclude administration of antitoxin. Equine botulinum antitoxin may be obtained from the Centers for Disease Control and Prevention (CDC) through the state health department which can significantly prevent worsening of botulism and may shorten its presentation if given early. Equine-derived heptavalent botulinum antitoxin (BAT) is the treatment of choice for pediatric and adult botulism which is available from the CDC. BAT contains antitoxin against all seven botulinum types A-G. BAT stops toxemia and ends further uptake of botulinum toxin. The CDC Emergency Operations Center may be contacted for botulism consultation and information regarding antitoxin.

Human-derived antitoxin or intravenous Human Botulism Immune Globulin (BIG-IV or Baby BIG) is the antitoxin of choice for infant botulism. Baby BIG is licensed for infant botulism due to *C. botulinum* toxin type A or B and is available through the California State Health Department (► www.infantbotulism.org; 510-231-7600). Baby BIG has been reported to significantly decrease the number of days of intensive care unit stay as well as total length of hospitalization.

Table 26.17 summarizes the different treatment regimens for botulisms.

Recovery from botulism takes several weeks to months. Complications include fatigue and shortness of breath for years and even death in 5% of patients. Mortality is associated from consequences of long-term paralysis or with respiratory failure.

## Chapter 29

### Case 1

1. The internal jugular central venous catheter is promptly removed, and she is treated with intravenous vancomycin.

2. Vancomycin would be effective, but its use should be reserved for the treatment of infections caused by methicillin-resistant *Staphylococcus aureus.* Methicillin is not a treatment option for methicillin-susceptible *S. aureus* because it has not been manufactured for use in clinical medicine for many years. Antibiotic susceptibility testing of *S. aureus* does not actually include methicillin, yet the terms methicillin-susceptible *S. aureus* (MSSA) and methicillin-resistant *S. aureus* (MRSA) are widely used.

Antibiotic susceptibility testing is performed using the related beta lactamase penicillin, oxacillin, so the more accurate terminology would be oxacillin-susceptible or resistant-susceptible *S. aureus* (OSSA or ORSA). While more accurate, and almost synonymous with MSSA and MRSA, use of the terms OSSA and ORSA has never gained traction.

All oxacillin susceptible isolates of *S. aureus* are also susceptible to methicillin, nafcillin, and cefazolin (a first-generation cephalosporin), so laboratory testing for each one individually is unnecessary. Antibiotic treatment for the patient under discussion should be switched from vancomycin to nafcillin, oxacillin, or cefazolin.

3. Treatment should continue for 10–14 days from the time of the first negative blood culture.

4. Persistent bacteremia despite the use of antibiotics that should be effective indicates the presence of an ongoing source, such as an abscess. Search for complications and metastatic foci of infection such as endocarditis, septic thrombophlebitis, osteomyelitis, pyomyositis.

### Case 2

1. As part of his fever evaluation, blood cultures should be collected from a peripheral vein and from his catheter. He has fever and neutropenia so broad spectrum, empiric intravenous antibiotics are necessary. The boy is treated empirically with vancomycin and cefepime.

2. Most coagulase negative staphylococci, including *Staphylococcus epidermidis,* are resistant to methicillin, so treatment with vancomycin is typically needed. Occasionally one will encounter a penicillin- or oxacillin-susceptible isolate. In those instances, it is not only appropriate, but it is preferred that the more narrow spectrum penicillin be used instead of vancomycin.

For the patient under discussion, the isolate is resistant to penicillin and oxacillin. In an attempt to salvage, rather than remove the device, his treatment included both intravenous vancomycin and vancomycin lock therapy for 10–14 days. The salvage effort was successful.

3. The catheter would need to be removed.

**Case 3**

1. He is at high risk for fungal infection. Blood cultures are positive for *Candida albicans.*

2. The PICC should be removed immediately. The antifungal treatment of choice for invasive candidiasis in this population is intravenous amphotericin B deoxycholate.

3. A lumbar puncture should be done to evaluate for meningeal involvement. In addition, ultrasonography of the abdomen, an echocardiogram, and a careful ophthalmologic examination should be performed to identify metastatic foci of infection.

## Chapter 30

1. A

2. C

3. B

4. D

## Chapter 32

1. This clinical scenario is common and can be difficult to clarify. Repeat infection with *Borrelia burgdorferi* is well-documented, and positive serology is unfortunately not protective. Because of this, serologic testing for Lyme disease is likely to be unreliable in this patient with a relatively recent history of Lyme arthritis, and so joint-fluid aspiration for PCR might be appropriate to test for a new infection. Because the symptoms were absent for several months, it is unlikely to be treatment-resistant arthritis due to persistent autoantibodies. It may be another Lyme infection, or it may be a different diagnosis entirely. Testing for other causes of arthritis, such as septic arthritis, post-streptococcal arthritis, rheumatoid arthritis, or assessing for a simple traumatic injury might be appropriate. Anticipatory guidance should include an explanation that after treatment for Lyme disease, the organism appears to be eradicated and does not persist, and that serology is often unhelpful after a proven case of Lyme disease in diagnosing future infections. In the situation where arthritis symptoms do persist after treatment for Lyme disease, it should be discussed that the symptoms are not due to persistent infection, but rather an immune response in the joint capsule that should improve with time. Symptomatic management with nonsteroidal anti-inflammatory drugs, steroid injections, or even a joint aspiration just to remove fluid may all help with joint pain and inflammation.

2. New guidelines and recommendations in the field of Lyme disease apply to this patient. Firstly, oral doxycycline is now considered as an option for Lyme meningitis, without signs of encephalitis. Treatment outcomes are identical to patients treated with intravenous ceftriaxone. Further to that, the duration of therapy is no longer thought to be required to be 28 days, but that 14 days may be sufficient. Lastly, doxycycline no longer has a concern for dental staining in children under the age of 8 years. As such, it would not be unreasonable to offer a 14-day course of oral doxycycline in this 5-year-old patient. However, parents or practitioners may feel uncomfortable with this option, due to the dramatic change in practice. IV ceftriaxone does have a long track record of success in treating Lyme meningitis. The risks of having a percutaneous line placed include thrombosis, line breakage, bleeding, or infection and should be placed against the benefits of once-daily reliable dosing. Risks from a percutaneous line appear to increase with time, so a 14-day course might be an appropriate plan. Conversely, young active children may not safely tolerate such IV access for a prolonged period. Amoxicillin should be discussed as part of the exercise, as it would normally be recommended in this age group, but learners should be aware that amoxicillin has not been studied in the context of treating Lyme meningitis, and cannot at this time be recommended for this indication. It should be noted also that oral doxycycline does itself carry risks of photosensitivity reactions and esophagitis or gastritis, which can adversely affect adherence to therapy.

3. There are multiple explanations for the continued fevers in this child, but of all of them, Lyme disease may be the least likely. He was appropriately treated with amoxicillin for erythema migrans, and so persistent fevers would strongly suggest an alternative explanation. Such explanations would include other tick-borne infections such as anaplasma or Babesia, neither of which would be treated by the amoxicillin that he had received, or non-tick-borne infections. Epstein-Barr virus and Cat-scratch disease (caused by *Bartonella henselae*) are common causes of persistent febrile illness in young children. While all of these can be diagnosed with serology or PCR, such testing may not provide rapid results (with the exception perhaps of the Monospot test for EBV, which is relatively insensitive at this age). Microscopic examination of the blood smear might reveal morulae of anaplasmosis, or the "Maltese Cross" intra-erythrocytic parasites of Babesia, but requires an experienced

laboratory worker. Basic blood work might reveal evidence for these infections: Anaplasma is associated with a leukopenia and thrombocytopenia, and hyponatremia. Babesia infection may demonstrate anemia. EBV infection may show elevated liver enzyme levels, lactate dehydrogenase, and atypical lymphocytes. If anaplasmosis is suspected, treatment with doxycycline is reasonable before serologic or PCR testing confirms the diagnosis.

## Chapter 34

1. 3
2. 3
3. 5
4. 4
5. 4

## Chapter 35

1. C
2. E
3. A
4. B
5. D
6. B
7. A
8. B
9. D
10. A

## Chapter 36

1. b. The answer is b. The next best step would be to obtain a peripheral blood smear to evaluate for any trypomastigotes, and confirm the diagnosis of acute Chaga's disease. After confirmation one would begin the treatment regimen with Benznidazole. Nifurtimox is also a possible pharmacological intervention but studies have shown that benznidazole is better tolerated. ELISA/antibody testing would be a better option given chronic Chaga's disease when the parasite is far less detectable in the peripheral blood as compared to acute Chaga's disease. An abdominal CT is out of scope for the patient's complaints.
2. c. The answer is c. There is currently no available vaccine to prevent infection with *T. cruzi* due to parasite antigenic shift and mimicry. The parasite is transmitted by the Triatomine vector to the host through the feces not the saliva.

## Chapter 37

1. b. This patient likely has leptospirosis and needs to receive rapid treatment. Furthermore, his cough suggests pulmonary involvement and CXR should be evaluated for pulmonary hemorrhage.
2. c. Conjunctival suffusion, particularly given the patient's history and myalgia localized to his calf, is indicative of leptospirosis. Begin treatment on oral amoxicillin after taking blood samples to be sent to the CDC. Make patient aware of complications to look out for, and tell him to report to the emergency room if he develops severe symptoms.

## Chapter 38

1. A
2. C

## Chapter 39

1. A, C, and D are all appropriate answers. Any patient with past travel to or emigration from an endemic country presenting with unexplained neurological pathology (most often seizures, but can include meningitis, CN palsies, and ocular deficits especially in NPNCC) should have neurocysticercosis included in their differential (A and C). D is a correct answer because the patient likely emigrated to the United States and has the classic presentation of neurocysticercosis. Although it is possible that this patient may have neurocysticercosis, it is extremely unlikely due to her brief travel history to a very well-developed tourist hub and her non-NCC specific symptoms.
2. E is the correct response. Humans can acquire neurocysticercosis by ways of autoinoculation (fecal-oral) or by ingestion of the eggs from a person with taeniasis through poor hand-hygiene. Human

ingestion of undercooked pork may cause taeniasis if the pork is infected with cysticerci, but not neurocysticercosis. A patient with any type of cysticercosis cannot transmit the parasite *unless* they also have taeniasis: cysticercosis in humans is an accidental infection that ends the life cycle of the parasite.

**Down**

1. proglottid
2. human
3. cysticercus
4. taeniaisis

**Across**

5. neurocysticercosis
6. oncosphere
7. seizures

## Chapter 41

Question 1 - Answer: D

Although it is possible that the patient has any of the available answer choices, when evaluating the patient's presentation and pertinent history, option D is the best choice. When considering acute HIV seroconversion, painful oral ulcers can help distinguish this diagnosis from the rest of the differential diagnoses. Infectious mononucleosis can present with fever, pharyngitis, tonsillitis, lymphadenopathy, and a maculopapular rash, but oral ulcers would be atypical. Hodgkin's lymphoma can present in young adults with fever, weight loss, night sweats, pruritus, and lymphadenopathy, but pharyngitis, oral ulcers, and a rash would make this option less likely. Streptococcal pharyngitis can present with fever, tonsillar exudate, pharyngitis, a rash, and tender cervical lymphadenopathy; however, it would be atypical to see oral ulcers here as well. Lastly, primary syphilis can present with a painless chancre (which can occur anywhere on the body, including the oropharynx), and secondary syphilis can present with pharyngitis, lymphadenopathy, and a rash although systemic symptoms like fever, fatigue, and myalgia are somewhat less common. HIV acute seroconversion can mirror a number of other diagnoses, and thus it is important to keep this in your differential diagnosis.

Question 2 – Answer C

In early HIV, there is a period of intense and rapid viral replication which results in high viral loads that can be above 100,000 viral copies/ml. During this period there is also infection of CD4+ T cells, with their total numbers remaining normal or decreasing transiently. Of the available options, only choice C reflects the normal CD4+ T-cell count and high HIV viral load typically seen during acute HIV infection.

Question 3 – Answer A

When ART was first introduced for treatment of HIV, the ideal time to start therapy was unknown. Significant improvement was noted in patients who had CD4+ T-cell counts less than 350 cells/mm$^3$; however, it was unclear if patients with preserved CD4+ T-cell counts would benefit from treatment. Additionally, toxicities were prevalent with all of the early treatment options. Although the patient in the vignette has a CD4+ T-cell count that is within the normal range, he would benefit from starting therapy as soon as possible. Treatment is predicted to reduce his risk for disease progression and reduce his HIV reservoir. Additionally, the risk for transmission to his partner is significantly reduced once his viremia is suppressed. PrEP should also be considered for his partner.

Question 4 – Answer B

While new or recurrent symptoms, including fever, cough, and worsening findings on chest imaging, should prompt an assessment for all possible causes, this patient is likely to have immune reconstitution inflammatory syndrome. Her symptoms improved after starting therapy for tuberculosis and HIV but recurred about 4 weeks later.

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# B



# C

# D

# E



# F



# G



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# K



# L

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# N

# O



# P

# R



# S

# T



# U



# V



# W



# Y



# Z