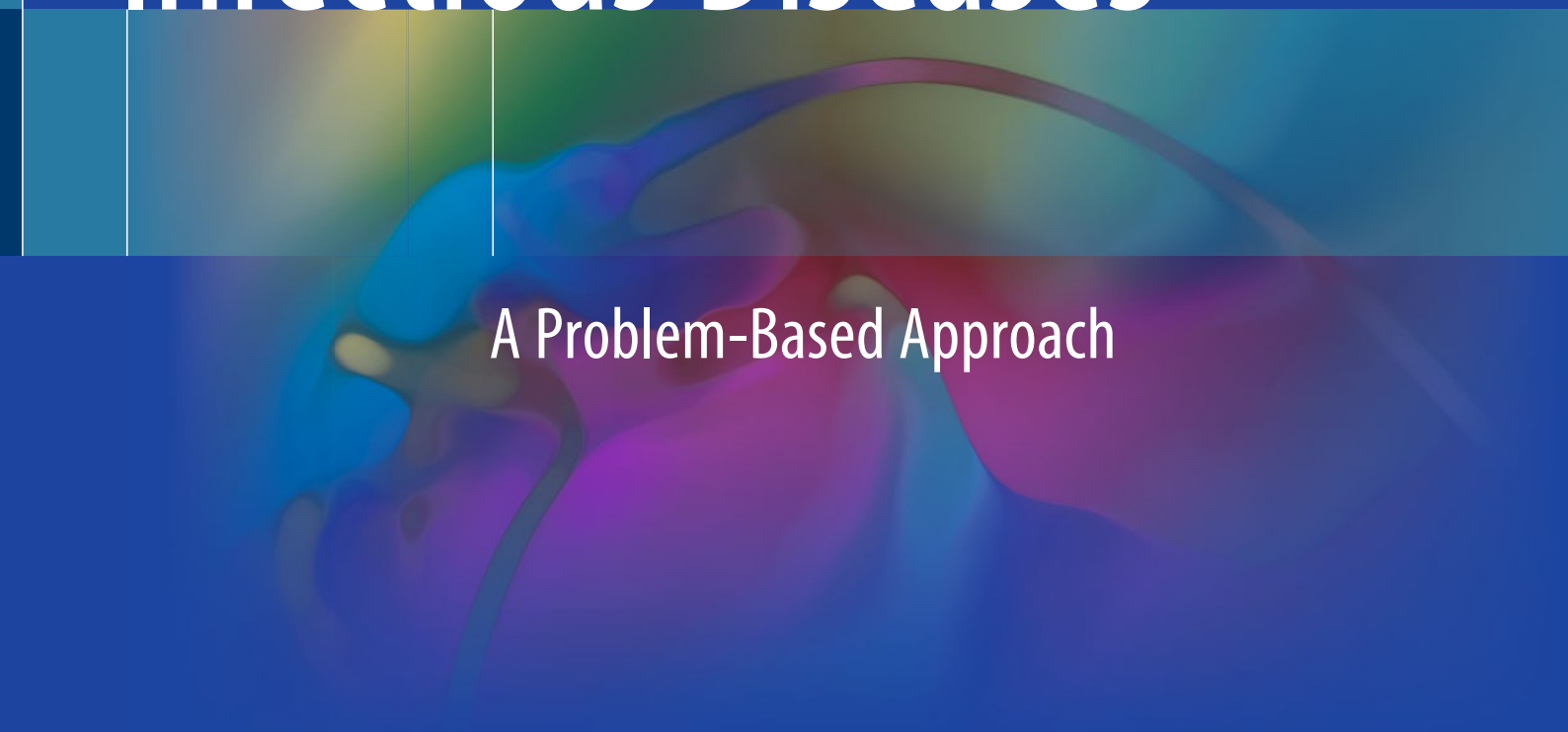
Joseph Domachowske
Editor

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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1

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

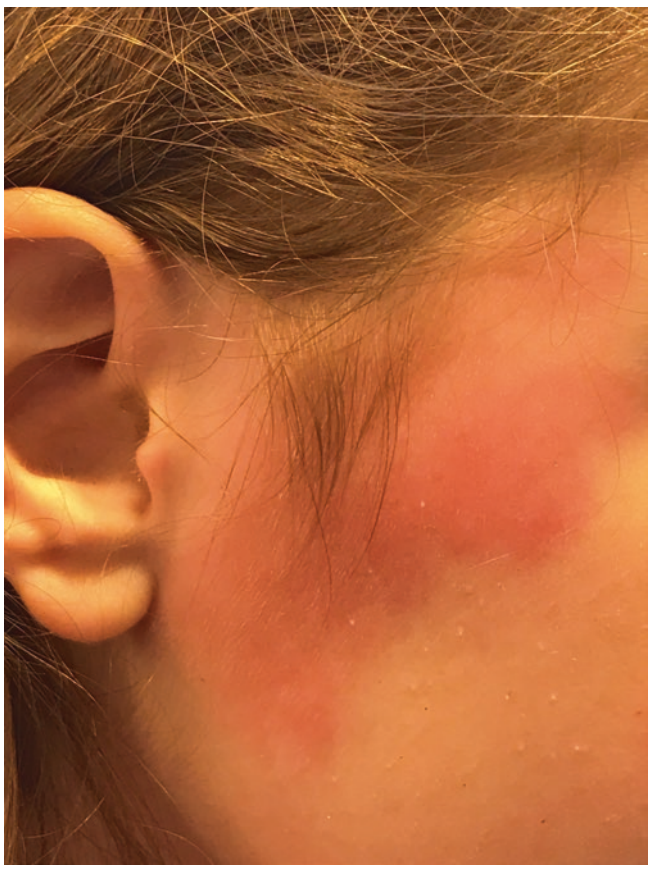

Fig. 1.1 Facial cellulitis secondary to *S. pyogenes*. Note the ill-defined borders of erythema. (Image provided courtesy of Dr. Jennifer Nead)

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 *Includes coverage against S. pyogenes and MSSA*	
Outpatient Cephalexin Dicloxacillin Clindamycin	**Inpatient** Cefazolin Oxacillin or nafcillin Clindamycin
Purulent cellulitis *Includes coverage against S. pyogenes, MSSA, and MRSA*	
Outpatient Clindamycin Trimethoprim/sulfamethoxazole (TMP-SMX) or doxycycline *and* a β-lactam class antibiotic (e.g., penicillin, amoxicillin, cephalexin) Linezolid Note: Monotherapy with TMP-SMX or doxycycline does not provide adequate coverage against *S. pyogenes*	**Inpatient** Clindamycin Vancomycin Linezolid
Abscess *Includes coverage against MSSA and MRSA*	
Outpatient Clindamycin Trimethoprim/sulfamethoxazole (TMP-SMX) Doxycycline (or minocycline) Linezolid	**Inpatient** Clindamycin Vancomycin 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 Sharply demarcated superficial skin infection of the upper dermis and superficial lymphatics 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 Note: In contrast to cellulitis, erysipelas is a more superficial infection with raised and well-demarcated borders	Systemic antibiotics If bullous erysipelas is present, include coverage against *Staphylococcus aureus*
Impetigo: Fig. 1.3 Highly contagious, localized superficial skin infection Nonbullous impetigo is seen in 70% of cases, and bullous impetigo is seen in 30% of cases Most common bacterial skin infection in children with peak incidence among children between ages 2 and 5	Nonbullous impetigo: MSSA and/or *Streptococcus pyogenes* Bullous impetigo: MSSA	Nonbullous impetigo: Maculopapular lesions progress to vesicles which rupture and leave superficial honey crusted lesions; common locations are face and extremities 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 Systemic antibiotic in outbreak settings or if lesions are numerous, widespread, or associated with large bullae Consider MRSA coverage if unresponsive to first-line treatment
Folliculitis Superficial skin infection in which hair follicle inflammation leads to a pus collection in the epidermis More common in adolescents and adults	MSSA, MRSA 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 Topical antibiotic such as mupirocin Systemic antibiotic for severe cases
Furuncle (boil) Folliculitis extends into the subcutaneous tissue where a small abscess forms 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 I&D (see abscess management in the text)
Carbuncle Collection of adjacent furuncles connected by sinus tracts with multiple drainage points More common in adolescents and adults	MSSA, MRSA	Organized group of adjacent furuncles with pus draining from multiple hair follicle sites	Warm moist compresses I&D (see abscess management in the text)
Necrotizing soft tissue infection Necrotizing infection involving any of the following: dermis, subcutaneous tissue, superficial fascia, deep fascia, or muscle	*Streptococcus pyogenes* **or** 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 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].

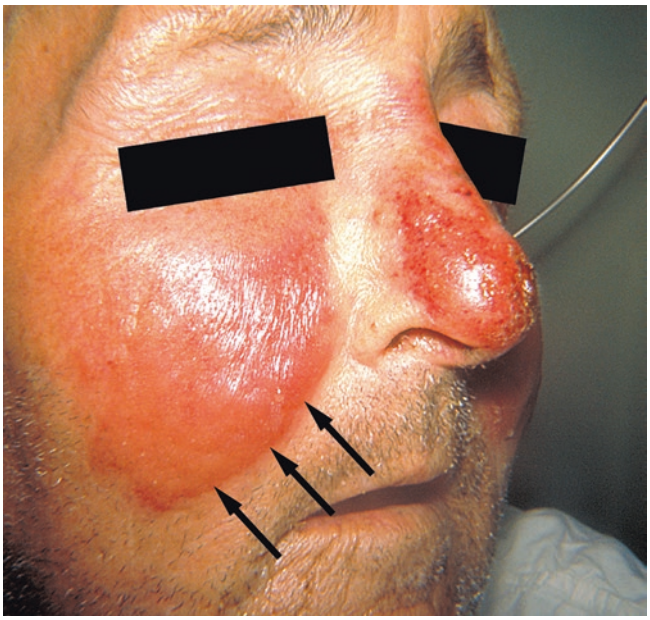

Fig. 1.2 Facial erysipelas secondary to infection with *S. pyogenes*. Note the sharply defined raised borders (arrows). (Reprinted from the Centers for Disease Control and Prevention Public Health Image Library. Image ID#2874; ► https://phil.cdc.gov/phil/details.asp)

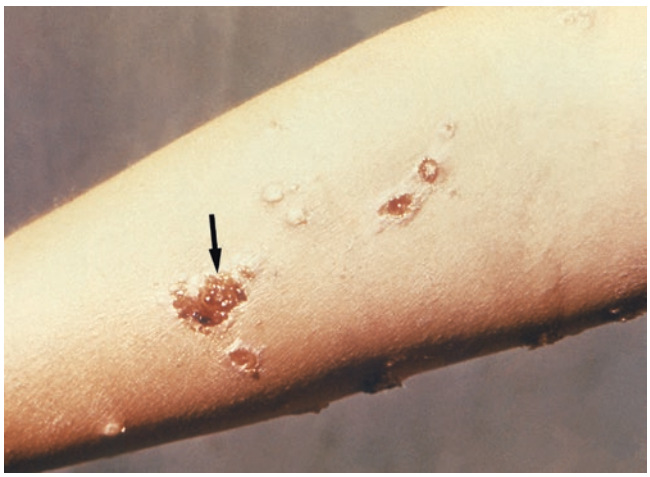

Fig. 1.3 Impetigo secondary to infection with *S. pyogenes*. Note the appearance of honey-colored crusting (arrow). (Reprinted from the Centers for Disease Control and Prevention Public Health Image Library.Image ID#14927; ► https://phil.cdc.gov/phil/details.asp)

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

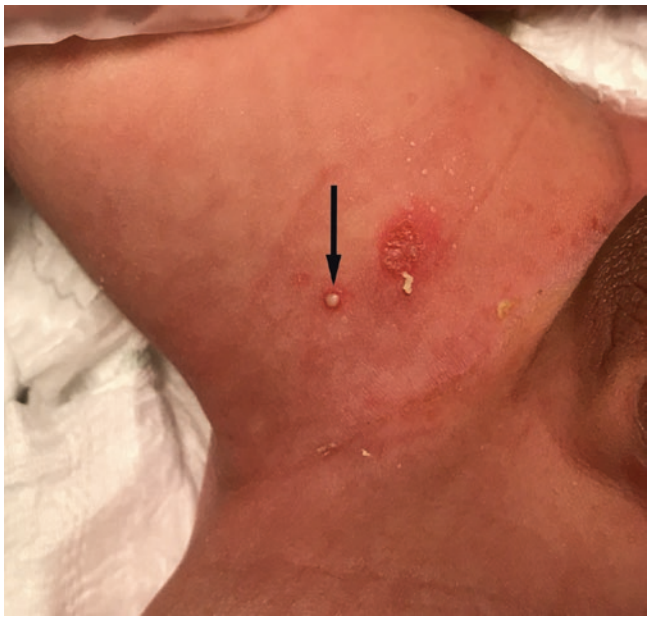

Fig. 1.4 Superficial pustule caused by methicillin susceptible *Staphylococcus aureus* associated with minimal surrounding erythema. (Image provided courtesy of Dr. Jennifer Nead)

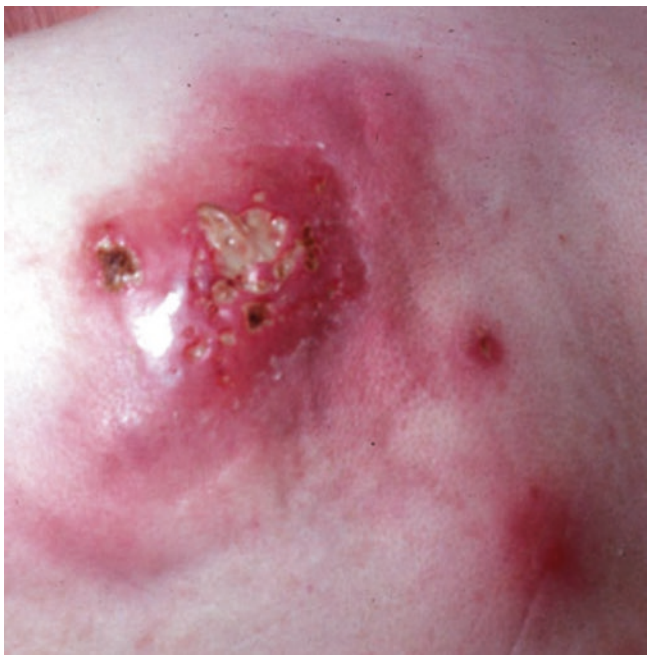

Fig. 1.5 Staphylococcal carbuncle. (Image provided by Dr. Joseph Domachowske)

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].

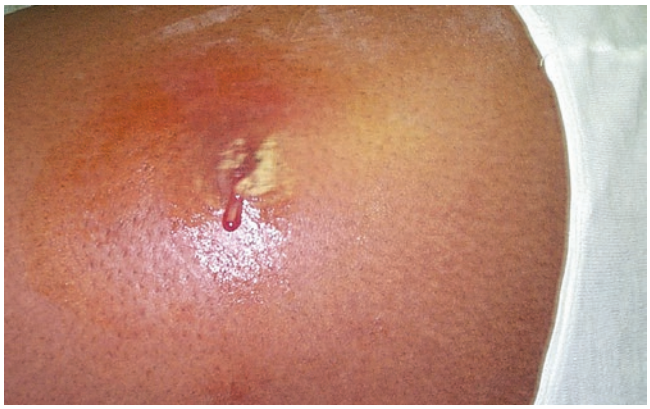

Fig. 1.6 Left thigh abscess with spontaneous drainage of serosanguinous fluid, caused by methicillin-resistant *Staphylococcus aureus*. (Centers for Disease Control and Prevention (CDC) Public Health Image Library (PHIL). Image ID#7826; ► https://phil.cdc.gov/phil/details.asp)

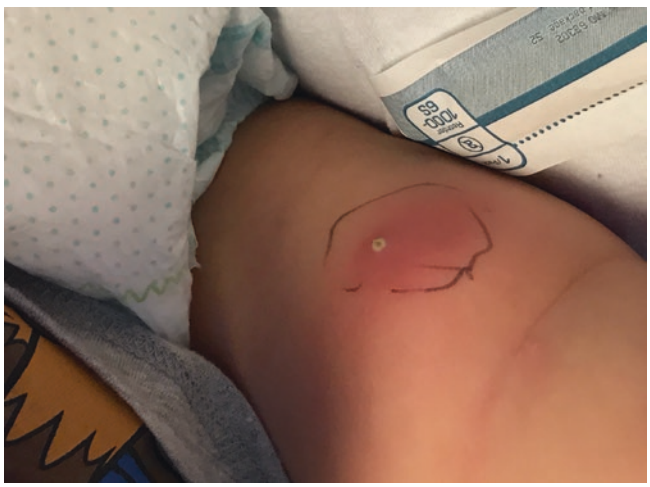

Fig. 1.7 Cutaneous pustule with surrounding cellulitis. On palpation, fluctuance was noted, heralding the presence of a large, deep soft tissue abscess. An I&D was performed. Cultures of the infected material grew methicillin susceptible *Staphylococcus aureus*. (Image provided courtesy of Dr. Jennifer 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 *Capnocytophaga canimorsus* *Streptococcus* species *Staphylococcus* species *Neisseria* species *Corynebacterium* species *Moraxella* species	*Fusobacterium* species *Bacteroides* species *Porphyromonas* species *Prevotella* species *Cutibacterium* species *Peptostreptococcus* species	Worldwide, the majority of human rabies cases occur after dog bites. Although rare, transmission of *Leptospira* species and *Francisella tularensis* has been reported after dog bites
Cat	*Pasteurella* species *Streptococcus* species *Staphylococcus* species *Moraxella* species *Neisseria* species *Corynebacterium* species *Enterococcus* species *Bacillus* species	*Fusobacterium* species *Bacteroides* species *Porphyromonas* species *Veillonella* species *Prevotella* species *Cutibacterium* species	*Bartonella henselae* and *Bartonella quintana* may be transmitted via a cat scratch or bite. Rarely, *Yersinia pestis* (cause of bubonic plague) and *Francisella tularensis* may be transmitted by cat bites
Human	*Eikenella corrodens* *Streptococcus* species *Staphylococcus* species *Haemophilus* species	*Fusobacterium* species *Peptostreptococcus* species *Prevotella* species *Porphyromonas* species *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)* 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. *Chlamydophila psittaci* may be transmitted through bites and may lead to psittacosis. 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 *Streptococcus anginosus* and *Streptococcus mutans* may cause palpable gas in subcutaneous tissue similar to gas gangrene 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 *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. *Rhodococcus equi* is an important pathogen in immunocompromised patients that causes pneumonia and meningitis. *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. 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 Transmission of *Leptospira* species occurs when bite wounds come into contact with urine from infected animals or soil that is contaminated with infected urine Tularemia resulting from transmission of F*rancisella tularensis* after hamster bites has been reported Lymphocytic choriomeningitis virus may be transmitted after rodent bites. Very rarely, hantavirus may be transmitted after rodent bites
Sharks	*Vibrio* species are the most commonly reported pathogens. 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.