cerebrospinal fluid shunt infection. *J Neurosurg Pediatr*. 2014;14(suppl 1):60–71.

81. Wang JH, Lin PC, Chou CH, et al. Intraventricular antimicrobial therapy in postneurosurgical gram-negative bacillary meningitis or ventriculitis: a hospital-based retrospective study. *J Microbiol Immunol Infect*. 2014;47: 204–210.
82. Wilkie MD, Hanson MF, Statham PF, et al. Infections of cerebrospinal fluid diversion devices in adults: the role of intraventricular antimicrobial therapy. *J Infect*. 2013;66:239–246.
83. Ng K, Mabasa VH, Chow I, et al. Systematic review of efficacy, pharmacokinetics, and administration of intraventricular vancomycin in adults. *Neurocrit Care*. 2014;20:158–171.
84. Imberti R, Cusato M, Accetta G, et al. Pharmacokinetics of colistin in cerebrospinal fluid after intraventricular administration of colistin methanesulfonate. *Antimicrob Agents Chemother*. 2012;56:4416–4421.
85. Tangden T, Enblad P, Ullberg M, et al. Neurosurgical gram-negative bacillary ventriculitis and meningitis: a retrospective study evaluating the efficacy of intraventricular gentamicin therapy in 31 consecutive cases. *Clin Infect Dis*. 2011;52:1310–1316.
86. Ziai WC, Lewin JJ 3rd. Improving the role of intraventricular antimicrobial agents in the management of meningitis. *Curr Opin Neurol*. 2009;22:277–282.
87. LeBras M, Chow I, Mabasa VH, et al. Systematic review of efficacy, pharmacokinetics, and administration of intraventricular aminoglycosides in adults. *Neurocrit Care*. 2016;25:492–507.
88. Pfausler B, Spiss H, Beer R, et al. Treatment of staphylococcal ventriculitis associated with external cerebrospinal fluid drains: a prospective randomized trial of intravenous compared with intraventricular vancomycin therapy. *J Neurosurg*. 2003;98:1040–1044.
89. Remes F, Tomas R, Jindrak V, et al. Intraventricular and lumbar intrathecal administration of antibiotics in postneurosurgical patients with meningitis and/or ventriculitis in a serious clinical state. *J Neurosurg*. 2013;119:1596–1602.
90. Wilkie MD, Hanson MF, Statham PF, et al. Infections of cerebrospinal fluid diversion devices in adults: the role of intraventricular antimicrobial therapy. *J Infect*. 2013;66:239–246.
91. Shah SS, Ohlsson A, Shah VS. Intraventricular antibiotics for bacterial meningitis in neonates. *Cochrane Database Syst Rev*. 2012;(7):CD004496.
92. Cook AM, Mieure KD, Owen RD, et al. Intracerebroventricular administration of drugs. *Pharmacotherapy*. 2009;29:832–845.
93. Brown EM, Edwards RJ, Pople IK. Conservative management of patients with cerebrospinal shunt infections. *Neurosurgery*. 2006;58:657–665.
94. The management of neurosurgical patients with postoperative bacterial or aseptic meningitis or external ventricular drain-associated ventriculitis. Infection in Neurosurgery Working Party of the British Society for Antimicrobial Chemotherapy. *Br J Neurosurg*. 2000;14:7–12.
95. Chen K, Wu Y, Wang Q, et al. The methodology and pharmacokinetics study of intraventricular administration of vancomycin in patients with intracranial infections after craniotomy. *J Crit Care*. 2015;30:218.e1–218.e5.
96. Arnell K, Enblad P, Wester T, et al. Treatment of cerebrospinal fluid shunt infections in children using systemic and intraventricular antibiotic therapy in combination with externalization of the ventricular catheter: efficacy in 34 consecutively treated patients. *J Neurosurg*. 2007;107(suppl 3):213–219.
97. Williamson JC, Glazier SS, Peacock JE Jr. Successful treatment of ventriculostomy-related meningitis caused by vancomycin-resistant *Enterococcus* with intravenous and intraventricular quinupristin/dalfopristin. *Clin Neurol Neurosurg*. 2002;104:54–56.
98. Cruciani M, Navarra A, Di Perri G, et al. Evaluation of intraventricular teicoplanin for the treatment of neurosurgical shunt infections. *Clin Infect Dis*. 1992;15:285–289.
99. Erritouni M, Ktaich N, Rahal JJ, et al. Use of daptomycin for the treatment of methicillin-resistant coagulase-negative staphylococcal ventriculitis. *Case Rep Med*. 2012;2012:593578.
100. Elvy J, Porter D, Brown E. Treatment of external ventricular drain-associated ventriculitis caused by *Enterococcus faecalis* with intraventricular daptomycin. *J Antimicrob Chemother*. 2008;61:461–462.
101. Jaspan HB, Brothers AW, Campbell AJ, et al. Multidrug-resistant *Enterococcus faecium* meningitis in a toddler: characterization of the organism and successful treatment with intraventricular daptomycin and intravenous tigecycline. *Pediatr Infect Dis J*. 2010;29:379–381.
102. Mueller SW, Kiser TH, Anderson TA, et al. Intraventricular daptomycin and intravenous linezolid for the treatment of external ventricular-drain-associated ventriculitis due to vancomycin-resistant *Enterococcus faecium*. *Ann Pharmacother*. 2012;46:e35.
103. Katragkou A, Roilides E. Successful treatment of multidrug-resistant *Acinetobacter baumannii* central nervous system infections with colistin. *J Clin Microbiol*. 2005;43:4916–4917.
104. Falagas ME, Bliziotis IA, Tam VH. Intraventricular or intrathecal use of polymyxins in patients with gram-negative meningitis: a systematic review of the available evidence. *Int J Antimicrob Agents*. 2007;29: 9–25.
105. Rodriguez Guardado A, Blanco A, Asensi V, et al. Multidrug-resistant *Acinetobacter meningitis* in neurosurgical patients with intraventricular catheters: assessment of different treatments. *J Antimicrob Chemother*. 2008;61:908–913.
106. Nelson JD. Cerebrospinal fluid shunt infections. *Pediatr Infect Dis J*. 1984;3:30–32.
107. James HE, Walsh JW, Wilson HD, et al. Prospective randomized study of therapy in cerebrospinal fluid shunt infection. *Neurosurgery*. 1980;7:459–463.
108. Schreffler RT, Schreffler AJ, Wittler RR. Treatment of cerebrospinal fluid shunt infections: a decision analysis. *Pediatr Infect Dis J*. 2002;21:632–636.
109. Walters BC. Cerebrospinal fluid shunt infection. *Neurosurg Clin North Am*. 1992;3:387–401.
110. Pelegrin I, Lora-Tamayo J, Gomez-Junyent J, et al. Management of ventriculoperitoneal shunt infections in adults: analysis of risk factors associated with treatment failure. *Clin Infect Dis*. 2017;64:989–997.
111. Lyke KE, Obasanjo OO, Williams MA, et al. Ventriculitis complicating use of intraventricular catheters in adult neurosurgical patients. *Clin Infect Dis*. 2001;33:2028–2033.
112. Holloway KL, Barnes T, Choi S, et al. Ventriculostomy infections: the effect of monitoring duration and catheter exchange in 584 patients. *J Neurosurg*. 1996;85:419–424.
113. Wong GKC, Poon WS, Wai S, et al. Failure of regular external ventricular drain exchange to reduce cerebrospinal fluid infection: result of a randomized controlled trial. *J Neurol Neurosurg Psychiatry*. 2002;73:759–761.
114. Chapman PH, Borges LF. Shunt infections: prevention and treatment. *Clin Neurosurg*. 1985;32:652–664.
115. Simon TD, Mayer-Hamblett N, Whitlock KB, et al. Few patient, treatment, and diagnostic or microbiologic factors, except complications and intermittent negative cerebrospinal fluid (CSF) cultures during the first CSF shunt infection, are associated with reinfection. *J Pediatr Infect Dis Soc*. 2014;3:15–22.
116. Mobley LW 3rd, Doran SE, Hellbusch LC. Abdominal pseudocyst: predisposing factors and treatment algorithm. *Pediatr Neurosurg*. 2005;41:77–83.
117. Kashyap S, Ghanchi H, Minasian T, et al. Abdominal pseudocyst as a complication of ventriculoperitoneal shunt placement: review of the literature and a proposed algorithm for treatment using 4 illustrative cases. *Surg Neurol Int*. 2017;8:78.
118. Stone J, Gruber TJ, Rozzelle CJ. Healthcare savings associated with reduced infection rates using antimicrobial suture wound closure for cerebrospinal fluid shunt procedures. *Pediatr Neurosurg*. 2010;46:19–24.
119. Pirotte BJ, Lubansu A, Bruneau M, et al. Sterile surgical technique for shunt placement reduces the shunt infection rate in children: preliminary analysis of a prospective protocol in 115 consecutive procedures. *Childs Nerv Syst*. 2007;23:1251–1261.
120. Hill M, Baker G, Carter D, et al. A multidisciplinary approach to end external ventricular drain infections in the neurocritical care unit. *J Neurosci Nursing*. 2012;44:188–193.
121. Haines SJ, Walters BC. Antibiotic prophylaxis for cerebrospinal fluid shunts: a meta-analysis. *Neurosurgery*. 1994;34:87–92.
122. Langley JM, LeBlanc JC, Drake J, et al. Efficacy of antimicrobial prophylaxis in placement of cerebrospinal fluid shunts: metaanalysis. *Clin Infect Dis*. 1993;17:98–103.
123. Ratilal B, Costa J, Sampaio C. Antibiotic prophylaxis for surgical introduction of intracranial ventricular shunts. *Cochrane Database Syst Rev*. 2006;(3):CD005365.
124. Alleyne CH Jr, Hassan M, Zabramski JM. The efficacy and cost of prophylactic and periprocedural antibiotics in patients with external ventricular drains. *Neurosurgery*. 2000;47:1124–1127.
125. Poon WS, Ng S, Wai S. CSF antibiotic prophylaxis for neurosurgical patients with ventriculostomy: a randomized study. *Acta Neurochir Suppl (Wien)*. 1998;71:146–148.
126. Sonabend AM, Korenfeld Y, Crisman C, et al. Prevention of ventriculostomy-related infections with prophylactic antibiotics and antibiotic-coated external ventricular drains: a systematic review. *Neurosurgery*. 2011;68:996–1005.
127. Govender ST, Nathoo N, van Dellen JR. Evaluation of an antibiotic-impregnated shunt system for the treatment of hydrocephalus. *J Neurosurg*. 2003;99:831–839.
128. Pattavilakom A, Xenos C, Bradfield O, et al. Reduction in shunt infection using antibiotic impregnated CSF shunt catheters: an Australian prospective study. *J Clin Neurosci*. 2007;14:526–531.
129. Sciubba DM, Stuart RM, McGirt MJ, et al. Effect of antibiotic-impregnated shunt catheters in decreasing the incidence of shunt infection in the treatment of hydrocephalus. *J Neurosurg*. 2005;103:131–136.
130. Kan P, Kestle J. Lack of efficacy of antibiotic-impregnated shunt systems in preventing shunt infections in children. *Childs Nerv Syst*. 2007;23:773–777.
131. Ritz R, Roser F, Morgalla M, et al. Do antibiotic-impregnated shunts in hydrocephalus therapy reduce the risk of infection? An observational study in 258 patients. *BMC Infect Dis*. 2007;7:38.
132. Thomas R, Lee S, Patole S, et al. Antibiotic-impregnated catheters for the prevention of CSF shunt infections: a systematic review and meta-analysis. *Br J Neurosurg*. 2012;26:175–184.
133. Parker SL, Anderson WN, Lilienfeld S, et al. Cerebrospinal shunt infection in patients receiving antibiotic-impregnated versus standard shunts. *J Neurosurg Pediatr*. 2011;8:259–265.
134. Attenello FJ, Garces-Ambrossi GL, Zaidi HA, et al. Hospital costs associated with shunt infections in patients receiving antibiotic-impregnated shunt catheters versus standard shunt catheters. *Neurosurgery*. 2010;66:284–289.
135. Parker SL, McGirt MJ, Murphy JA, et al. Comparative effectiveness of antibiotic-impregnated shunt catheters in the treatment of adult and pediatric hydrocephalus: analysis of 12,589 consecutive cases from 287 hospital systems. *J Neurosurg*. 2015;122:443–448.
136. Zabramski JM, Whiting D, Darouiche RO, et al. Efficacy of antimicrobial-impregnated external ventricular drain catheters: a prospective, randomized, controlled trial. *J Neurosurg*. 2003;98:725–730.
137. Kestle JRW, Riva-Cambrin J, Wellons JC 3rd, et al. A standardized protocol to reduce cerebrospinal fluid shunt infection: the Hydrocephalus Clinical Research Network Quality Improvement Initiative. *J Neurosurg Pediatr*. 2011;8:22–29.
138. Kestle JR, Holubkov R, Douglas Cochrane D. A new Hydrocephalus Clinical Research Network protocol to reduce cerebrospinal fluid shunt infection. *J Neurosurg Pediatr*. 2016;17:391–396.
139. Flint AC, Rao VA, Renda NC, et al. A simple protocol to prevent external ventricular drain infections. *Neurosurgery*. 2013;72:993–999, discussion 999.
140. Flint AC, Toossi S, Chan SL, et al. A simple infection control protocol durably reduces external ventricular drain infections to near-zero levels. *World Neurosurg*. 2017;99:518–523.

Skin and Soft Tissue Infections

93 Cellulitis, Necrotizing Fasciitis, and Subcutaneous Tissue Infections

Mark S. Pasternack and Morton N. Swartz[a]

SHORT VIEW SUMMARY

Definition
- Skin and soft tissue infections are characterized by location, depth of infection, etiologic agent, and clinical setting and may result from either primary cutaneous inoculation or, less commonly, hematogenous seeding.
- *Impetigo* is a superficial crusting and at times bullous infection of the skin; localized progression into the dermis leads to ecthyma.
- *Folliculitis* is a localized infection of hair follicles, which can extend into subcutaneous tissue, resulting in furuncles. These, in turn, may coalesce, leading to carbuncle formation.
- *Erysipelas* is a rapidly progressive infection of the superficial dermis, with sharp erythematous borders; *cellulitis* reflects deeper dermal involvement.
- Necrotizing skin and soft tissue infections, including *necrotizing fasciitis,* are rare life-threatening infections, occur in a variety of clinical settings, and require prompt diagnosis and surgical intervention.

Epidemiology
- Significant skin and soft tissue infection may occur throughout the age spectrum. Minor local trauma as the initial pathogenic event is a common feature of these processes. Although invasive infections may occur in previously healthy individuals, a variety of systemic risk factors predispose individuals to these infections.

Microbiology
- Hemolytic streptococci and *Staphylococcus aureus,* including methicillin-resistant *S. aureus* (MRSA), are the most common causes of superficial cutaneous infection.
- Mixed infection of facultative gram-negative bacilli, anaerobes, and gram-positive organisms most frequently cause necrotizing infection, but group A streptococci, clostridia, and *Vibrio* species (as well as other facultative gram negatives) can also cause monomicrobial necrotizing fasciitis.
- A broad differential diagnosis must be considered in confronting infections in immunocompromised patients.

Diagnosis
- Most cutaneous infections are not associated with bacteremia, and diagnosis and empirical therapy are based on physical findings and clinical setting.
- In immunocompromised hosts, tissue biopsy for microbiologic and histologic study is critical to plan definitive therapy.

Therapy
- Oral therapy targeted against gram-positive pathogens is appropriate for mild disease, with close follow-up and revision of therapy for inadequate response. Parenteral therapy targeted more broadly against gram-positive organisms (including *S. aureus* and MRSA), gram-negative pathogens, and anaerobes is required in many settings of severe infection, particularly in compromised hosts.
- Necrotizing infections require urgent surgical débridement.
- Infections associated with toxic shock syndrome are treated with protein synthesis inhibitors such as clindamycin as an adjunctive measure to antibiotic treatment.

Prevention
- Good hygienic practices and attention to early therapy for superficial processes such as dermatophyte infection reduce the risk for cutaneous and soft tissue infection.
- Individuals with recurrent cellulitis may benefit from chronic antibiotic suppression.

CELLULITIS AND SUPERFICIAL INFECTIONS

Bacterial and mycotic infections, exclusive of those caused by the common dermatophytes, are discussed in this chapter. Classification of cutaneous infections on morphologic and clinical grounds can be very helpful in providing initial clues regarding the most likely responsible infectious agents (Table 93.1).

Primary Pyodermas

Impetigo

Impetigo is an initially vesicular, later crusted, superficial infection of the skin. Most cases occur in children. The annual incidence of impetigo is 1% to 2%, with annual summer epidemics.[1] There are both geographic and yearly variations in incidence related to the clonal spread of virulent or resistant pathogens.[2] Previously, group A streptococcus was the principal cause of impetigo and was isolated from about 80% of cases, either alone or mixed with *Staphylococcus aureus.*[3] In the past 20 years, group A streptococcus has been found less commonly (20%–30%) in impetigo and has been supplanted by *S. aureus,*[1–4] with a growing frequency of methicillin-resistant *S. aureus* (MRSA) isolates, although the relative frequency of these pathogens (alone or in mixed infection) varies among different populations.[5] Conceivably, the role of staphylococci may be somewhat overestimated because these organisms are common secondary invaders, and some strains produce bacteriocins that may impair the recovery of group A streptococci.

Pathologic Characteristics and Pathogenesis

Histopathologically, impetigo consists of superficial, intraepidermal, unilocular vesicopustules. In epidemiologic studies, group A streptococcal acquisition on normal skin antedates the appearance of impetigo by about 10 days.[3] During that time, minor trauma (e.g., insect bite, abrasion) or

[a]Morton N. Swartz, a long-time contributor to chapters in previous editions of *Principles and Practice of Infectious Diseases,* died on September 9, 2013.

TABLE 93.1 Classification of Bacterial and Mycotic Infections of the Skin

TYPE OF LESION	CAUSATIVE AGENTS
Primary Pyodermas	
Impetigo, bullous impetigo	*Staphylococcus aureus,* group A streptococci
Folliculitis	*S. aureus, Candida, Pseudomonas aeruginosa, Malassezia furfur, Pityrosporum ovale*
Furuncles and carbuncles	*S. aureus*
Paronychia	*S. aureus,* group A streptococci, *Candida, P. aeruginosa*
Ecthyma	Group A streptococci
Chancriform lesions	*Treponema pallidum, Haemophilus ducreyi, Sporothrix, Bacillus anthracis, Francisella tularensis, Mycobacterium ulcerans, Mycobacterium marinum*
Erysipelas	Group A streptococci
Cellulitis	Group A or other streptococci, *S. aureus;* rarely, various other organisms
Membranous ulcers, including cutaneous diphtheria	*Corynebacterium diphtheriae*
Erythrasma	*Corynebacterium minutissimum*
Scarlet Fever Syndromes	
Scalded skin syndrome	*S. aureus* (phage group II)
Scarlet fever	Group A streptococci, rarely *S. aureus*
Toxic shock syndrome	*S. aureus* (pyogenic toxin-producing strains), *S. pyogenes*
Infectious Gangrene and Gangrenous Cellulitis	
Streptococcal gangrene and necrotizing fasciitis	Group A streptococci, mixed infections with Enterobacteriaceae and anaerobes
Progressive bacterial synergistic gangrene	Anaerobic streptococci plus a second organism (*S. aureus, Proteus*)
Gangrenous balanitis and perineal phlegmon	Group A streptococci, mixed infections with enteric bacteria (e.g., *Escherichia coli, Klebsiella*) and anaerobes
Gas gangrene, crepitant cellulitis	*Clostridium perfringens* and other clostridial species; *Bacteroides*, peptostreptococci, *Klebsiella, E. coli*
Gangrenous cellulitis in immunosuppressed patients	*Pseudomonas, Aspergillus,* agents of mucormycosis
Secondary Bacterial Infections Complicating Preexisting Skin Lesions	
Burns	*P. aeruginosa, Enterobacter,* various other gram-negative bacilli, various streptococci, *S. aureus, Candida, Aspergillus*
Eczematous dermatitis and exfoliative erythrodermas	*S. aureus,* group A streptococci
Chronic ulcers (varicose, decubitus)	*S. aureus,* streptococci, coliform bacteria, *P. aeruginosa,* peptostreptococci, enterococci, *Bacteroides, C. perfringens*
Dermatophytosis	*S. aureus,* group A streptococci
Traumatic lesions (e.g., abrasions, animal bites, insect bites)	*Pasteurella multocida, C. diphtheriae, S. aureus,* group A streptococci
Vesicular or bullous eruptions (varicella, pemphigus)	*S. aureus,* group A streptococci
Acne conglobata	*Propionibacterium acnes*
Hidradenitis suppurativa	*S. aureus, Proteus* and other coliforms, streptococci, peptostreptococci, *P. aeruginosa, Bacteroides*
Intertrigo	*S. aureus,* coliforms, *Candida*
Pilonidal and sebaceous cysts	Peptostreptococci, *Bacteroides,* coliforms, *S. aureus*
Pyoderma gangrenosa	*S. aureus,* peptostreptococci, *Proteus* and other coliforms, *P. aeruginosa*
Cutaneous Involvement in Systemic Bacterial and Mycotic Infections	
Bacteremias	*S. aureus,* group A streptococci (also other groups such as D), *Neisseria meningitidis, Neisseria gonorrhoeae, P. aeruginosa, Salmonella typhi, Haemophilus influenzae*
Infective endocarditis	Viridans-group streptococci, *S. aureus,* group D streptococci, and others
Fungemias	*Candida, Cryptococcus, Blastomyces dermatitidis, Fusarium*
Listeriosis	*Listeria monocytogenes*
Leptospirosis (Weil syndrome and pretibial fever)	*Leptospira interrogans* serotypes
Rat-bite fever	*Streptobacillus moniliformis, Spirillum minus*
Melioidosis	*Burkholderia pseudomallei*
Glanders	*Burkholderia mallei*
Carrión disease (verruga peruana)	*Bartonella bacilliformis*

Continued

TABLE 93.1 Classification of Bacterial and Mycotic Infections of the Skin—cont'd

TYPE OF LESION	CAUSATIVE AGENTS
Parainfectious and Postinfectious Nonsuppurative Complications	
Purpura fulminans (manifestation of disseminated intravascular coagulation)	Group A streptococci, *N. meningitidis, S. aureus,* pneumococci
Erythema nodosum	Group A streptococci, *Mycobacterium tuberculosis, Mycobacterium leprae, Coccidioides immitis, Leptospira autumnalis, Yersinia enterocolitica, Legionella pneumophila*
Erythema multiforme–like lesions (rarely), guttate psoriasis	Group A streptococci
Other Lesions	
Nodular lesions	*Candida, Sporothrix, S. aureus* (botryomycosis), *M. marinum, Nocardia brasiliensis, Leishmania brasiliensis*
Hyperplastic (pseudoepitheliomatous) and proliferative lesions (e.g., mycetomas)	*Nocardia, Pseudallescheria boydii, Blastomyces dermatitidis, Paracoccidioides brasiliensis, Phialophora, Cladosporium*
Vascular papules/nodules (bacillary angiomatosis, epithelioid angiomatosis)	*Bartonella henselae, Bartonella quintana*
Annular erythema (erythema chronicum migrans)	*Borrelia burgdorferi*

primary dermatoses predispose to the development of infected lesions. Impetigo is most common during hot, humid summer weather. Two to 3 weeks after skin acquisition of streptococci, pharyngeal colonization by the same organism occurs in about 30% of children with skin lesions. (The sporadic cases of facial impetigo occurring in cooler climates probably result from contiguous spread from an initial nasopharyngeal infection, and the serotypes involved are those commonly causing pharyngeal disease.) In staphylococcal impetigo (in which *S. aureus* is the only pathogen), skin infection follows nasal colonization.[5,6] Among returning travelers, impetigo is commonly associated with antecedent insect bites.[7]

Nonbullous impetigo caused by group A streptococcus (*Streptococcus pyogenes*) begins when the corneal layer of the epidermis is disrupted and the bacteria gain access to highly differentiated subcorneal keratinocytes. Impetigo strains, but not pharyngeal strains, of *S. pyogenes* preferentially bind to differentiated keratinocytes,[8] mediated by *S. pyogenes* M protein.[9] A number of additional surface proteins serve as adhesins and promoters of internalization within epithelial cells,[10] and their preferential expression accounts for the selective tropism observed among different *S. pyogenes* strains.[11,12] Staphylococcal infection usually develops after nasal or skin colonization. Bacteriocin production may inhibit competing commensal flora, and several virulence factors have been proposed to enhance adhesion to epithelial cells and to underlying matrix proteins.[13] Surprisingly, the production of exfoliative toxins A and B has been associated with both nonbullous and bullous impetigo; Panton-Valentine leukocidin is generally absent among staphylococcal impetigo isolates.[5] Impetigo is a highly communicable infection. Spread in families (particularly among preschool-age children) is facilitated by crowding and poor hygiene.

Clinical Manifestations

Streptococcal impetigo begins on exposed areas as small vesicles, sometimes with narrow inflammatory halos, that rapidly pustulate and readily rupture. The purulent discharge dries and forms the characteristic thick, golden-yellow, "stuck-on" crusts. Pruritus is common, and scratching of lesions can spread infection. Occasionally, large crusts are produced by coalescence of smaller pustules. The lesions remain superficial and do not ulcerate or infiltrate the dermis; mild regional lymphadenopathy is common. Healing generally occurs without scarring. The lesions are painless, and constitutional manifestations are minimal.

Laboratory Findings

Gram-stained smears of vesicles show gram-positive cocci. Culture of exudate beneath an unroofed crust reveals *S. aureus,* group A streptococci, or a mixture of streptococci and *S. aureus.* The anti–streptolysin O titer after streptococcal impetigo is scant, probably related to inhibition of streptolysin O by skin lipids at the infection site. In contrast, the anti–desoxyribonuclease B response readily occurs after streptococcal impetigo (with elevated titers in 90% of patients with nephritis complicating streptococcal skin infections).[14]

Etiologic Agents

The group A streptococci responsible for impetigo usually belong to different M serotypes from those of strains that produce pharyngitis. M surface proteins, which are key virulence factors, are encoded in *emm* genes. Five major *emm* chromosomal patterns (groups A through E) have been described based on nucleotide sequences encoding part of the peptidoglycan-spanning M protein domain.[15] Almost all group A streptococcal impetigo isolates belong to *emm* chromosomal patterns D and, to a lesser extent, E, whereas most isolates from patients with uncomplicated pharyngitis or acute rheumatic fever belong to *emm* chromosomal pattern group A, B, or C. Groups C and G streptococci may rarely cause impetigo; group B streptococci have been associated with impetigo in neonates. The rising incidence of MRSA impetigo has been associated with both hospital- and community-acquired strains.[5]

Differential Diagnosis

Although the initial vesicular lesions may resemble early varicella, the crusts of impetigo are darker brown and harder. The central clearing of a confluent cluster of lesions of impetigo may suggest tinea circinata but can be distinguished by the thick crusts, which are not formed in the fungus infection. When the vesicles of herpes simplex become turbid, they may resemble those of impetigo. Distinguishing between herpes simplex and impetigo is important because irritation from topical therapy may exacerbate primary herpes simplex lesions. Acute palmoplantar pustulosis, a sterile, idiopathic, self-limited pustular eruption on the palms and soles that sometimes occurs after pharyngitis, may initially resemble impetigo.[16] Localized acute pustular psoriasis may also be mistaken for impetigo. Primary cutaneous listeriosis, an occupational disease of veterinarians and farmers involved in calving, is characterized by papulovesicular and pustular lesions on the forearms that may resemble those of impetigo.[17] Atopic or contact dermatitis, discoid lupus erythematosus, and infestations such as scabies may mimic impetigo or develop secondary impetiginization.[18]

Presumptive Therapy

Penicillin was the classic drug of choice for the treatment of impetigo, because of the predominant role of group A streptococci and the subsequent risk for acute glomerulonephritis. Because mixed streptococcal-staphylococcal or staphylococcal impetigo is clinically indistinguishable from streptococcal impetigo, and because *S. aureus,* either alone or in concert with *S. pyogenes,* currently is the predominant cause of impetigo, primary therapy must be revised accordingly. Penicillinase-resistant oral penicillins (e.g., dicloxacillin or amoxicillin-clavulanate) or cephalosporins (e.g., cephalexin, cefadroxil) are generally effective for treating methicillin-sensitive strains of *S. aureus* as well as *S. pyogenes.* The relative incidence of MRSA (vs. methicillin-susceptible *S. aureus* [MSSA]) causing impetigo is not well established, and likely differs among different populations. Erythromycin or newer macrolides generally are reserved for β-lactam–allergic patients. The efficacy of

macrolides may be reduced in areas in which erythromycin-resistant staphylococci and streptococci are prevalent. Local care (removal of crusts by soaking with soap and water) is helpful. Patients with extensive disease should undergo wound culture and reevaluation after an initial trial of oral therapy. The presence of MRSA must be strongly considered if there is a poor initial response to therapy, even if no culture data are available, and empirical therapy must be broadened (see later). Co-trimoxazole has excellent activity against community-acquired MRSA, and in vitro data support its possible use against *S. pyogenes* as well, although clinical data are limited.[19] A recent review suggests that this agent is useful both for presumed *S. aureus* and *S. pyogenes* skin infections.[20] Clindamycin and macrolides have variable efficacy against many community-acquired MRSA isolates and often vary in distinct populations. Topical antibiotic therapy may be considered when treating limited impetigo, including that caused by MRSA.

Topical mupirocin ointment in a polyethylene glycol base is as effective as oral erythromycin for the treatment of impetigo[21] and is more effective when treating erythromycin-resistant *S. aureus.*[22] In the past decade, the incidence of mupirocin resistance among *S. aureus* isolates has been rising slowly but steadily.[23] A second topical antibiotic, retapamulin ointment, is approved for the treatment of impetigo. This is the first of a novel class of bacterial protein synthesis inhibitors (pleuromutilins) and is effective against *S. aureus* and *S. pyogenes* independent of other antibiotic susceptibilities.[24] Fusidic acid cream is available in Europe and is effective in treating childhood impetigo (primarily *S. aureus*), but rising resistance rates[2] and policies to restrict its applicability for systemic infection have limited its use. Gentle application of topical agents is important to minimize tissue maceration and spread of infection. Systemic therapy is preferred when treating widespread impetigo. Close follow-up of patients is important because of rising rates of resistance to these topical and systemic agents.

Mupirocin has also been used topically to eradicate MRSA from secondarily infected skin lesions and from colonized patients. However, because resistance in *S. aureus* strains has emerged sooner than anticipated after the introduction of mupirocin,[22] particularly when long-term therapy was used, prolonged administration should probably be avoided.

Bullous Impetigo

Clinical Manifestations

The bullous form of impetigo is caused by *S. aureus* of phage group II (usually type 71); it occurs principally in neonates and young children and accounts for about 10% of all cases of impetigo. The lesions begin as vesicles that turn into flaccid bullae initially containing clear yellow fluid. No erythematous areola is noted, and the Nikolsky sign is absent. The bullae quickly rupture, leaving a moist red surface, and then form thin, varnish-like light brown crusts. Bullous impetigo, like the staphylococcal scalded skin syndrome (SSSS) and the staphylococcal scarlatiniform syndrome, represents a cutaneous response to the two extracellular exfoliative toxins (ETA and ETB) produced by phage group II *S. aureus. S. aureus* isolates from patients with bullous impetigo uniformly carry these exfoliative toxins.[5,25] ETA is chromosomally encoded, and the heat-labile ETB is plasmid encoded. Both are glutamate-specific serine proteases that bind to and cleave desmoglein-1, a desmosomal transmembrane glycoprotein necessary for epidermal cell adhesion.[25,26] The toxins may act locally at the site of cutaneous infection to produce bullous impetigo or may spread systemically to cause generalized blistering when produced at a site of cutaneous *S. aureus* infection. Staphylococci are regularly isolated from the skin lesions of bullous impetigo. Streptococcal superinfection rarely complicates bullous impetigo, probably because type 71 strains of *S. aureus* produce a bacteriocin that inhibits streptococci. Fever and constitutional symptoms are uncommon, and healing occurs without scarring. Mild infections are often missed[27] and have even been misdiagnosed as nonaccidental scalds in young children.[28] Rarely, bullous impetigo has been attributed to group A streptococcal infection.

Presumptive Therapy

Extensive bullous impetigo caused by MSSA generally responds to treatment with a penicillinase-resistant penicillin agent (e.g., dicloxacillin, 25–50 mg/kg daily in divided doses orally every 6 hours for a child; or amoxicillin-clavulanic acid), cephalosporin (e.g., cephalexin, 25–50 mg/kg daily in divided doses orally every 8–12 hours for a child), or erythromycin or clindamycin for a penicillin-allergic patient. When MRSA is widespread in the community, culture and initial oral therapy with co-trimoxazole, clindamycin, or linezolid may be considered for mild-to-moderate disease, with initial intravenously administered vancomycin reserved for patients with widespread disease.

Staphylococcal Scalded Skin Syndrome

SSSS is the most severe and systemic manifestation of infection with *S. aureus* strains producing an exfoliative exotoxin; it is characterized by widespread bullae and exfoliation.[26,29] Pemphigus neonatorum (Ritter disease) is SSSS in the neonate. The more general term *toxic epidermal necrolysis* is often used to encompass both SSSS and a morphologically similar syndrome of various causes (drug reactions, viral illnesses; see Chapter 194). SSSS has been associated with both MSSA and MRSA.

Clinical Manifestations

SSSS usually occurs in younger children but can rarely develop in adults. Epidemics have occurred in neonatal nurseries.[30] SSSS begins abruptly (sometimes a few days after a recognized staphylococcal infection) with fever, skin tenderness, and a scarlatiniform rash. The Nikolsky sign can be demonstrated. Large, flaccid, clear bullae form and promptly rupture, resulting in the separation of sheets of skin. New bullae appear over a period of 2 to 3 days. Exfoliation exposes large areas of bright red skin surface (Fig. 93.1). Denuded surfaces are generally devoid of *S. aureus,* since exfoliative toxins are disseminated hematogenously from a primary infection. Indeed, *S. aureus* may be recovered from a distant site of infection or colonization. This is in contrast to the ready recovery of organisms from sites of localized bullous impetigo, where toxin is elaborated at the site of the lesion. In settings in which the diagnosis

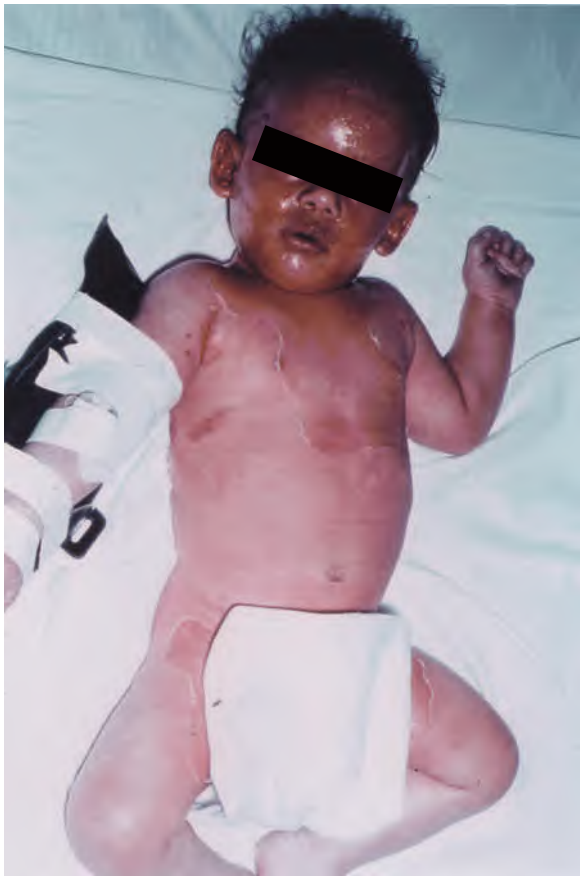

FIG. 93.1 Staphylococcal scalded skin syndrome in a young infant. Exfoliation has occurred on the face, chest, and groin, exposing areas of bright red skin surface.

of SSSS is uncertain, a biopsy obtained from an area of desquamation will demonstrate bland intraepidermal cleavage at the granular layer, which is distinct from the subepidermal separation observed in bullous disorders and toxic epidermal necrolysis. With appropriate fluid replacement and antimicrobial therapy, the skin lesions heal within 2 weeks, in contrast to drug-induced toxic epidermal necrolysis, in which recovery is more prolonged because the entire epidermis must be replaced and scarring is more frequent. The mortality rate from SSSS in children is less than 3% but is often higher in adults, many of whom have underlying immunodeficiency, renal failure, or other significant comorbidities.

Presumptive Therapy

Intravenous vancomycin is indicated for the initial treatment of SSSS because of the widespread staphylococcal infection and rapid progression of the skin lesions, particularly in settings such as a neonatal nursery and in communities with high rates of MRSA disease. Once MSSA is identified, intravenous nafcillin (100 mg/kg/day for neonates, 100–200 mg/kg/day for older children) is appropriate. Topical treatment consists of cool saline compresses. Systemic corticosteroids alone should not be used in the treatment of SSSS, although they may be indicated in therapy for drug-induced toxic epidermal necrolysis.

Staphylococcal Scarlet Fever

Staphylococcal scarlet fever is fundamentally a forme fruste of SSSS that does not progress beyond the initial stage of a generalized erythematous eruption. However, *S. aureus* enterotoxins (A through D) and toxic shock syndrome toxin 1 (TSST-1) are more frequently associated with staphylococcal scarlet fever than are ETA and ETB.[31] The rash is indistinguishable from that of scarlet fever, and Pastia lines can develop. However, pharyngitis is not usually present and an enanthem does not develop. Desquamation, beginning on the face and involving most of the body, occurs 2 to 5 days after onset of the scarlatiniform rash. Antibiotic treatment (penicillinase-resistant penicillins or alternative therapy effective against MRSA) is indicated.

Toxic Shock Syndrome

Toxic shock syndrome is another acute febrile illness with a generalized scarlatiniform eruption associated with *S. aureus* infection.[32] Other elements of the syndrome include (1) hypotension (shock), (2) functional abnormalities of three or more organ systems, and (3) desquamation in the evolution of the skin lesions[29,33] associated with the elaboration of TSST-1 or one of several staphylococcal enterotoxins. These exotoxins act as superantigens that activate large numbers of T cells, triggering systemic inflammation, distinct from the direct-acting exfoliative toxins responsible for bullous impetigo and SSSS (see Chapter 194).

Folliculitis

Folliculitis is a pyoderma located within hair follicles and the apocrine regions. The lesions consist of small (2–5 mm), erythematous, sometimes pruritic papules often topped by a central pustule and a fine surrounding collar of desquamation.[34] Sycosis barbae is a distinctive form of deep folliculitis, often chronic, that occurs on bearded areas. *S. aureus* is the usual cause of folliculitis. *Pseudomonas aeruginosa* (most often serotype O11) has been responsible for folliculitis acquired from swimming pools and whirlpools contaminated with large numbers of these organisms[35]; *Aeromonas* folliculitis has been reported rarely in similar settings. This type of skin infection produces pruritic, sometimes tender, papulourticarial lesions (appearing within 48 hours after exposure) that eventuate in pustule formation. Lesions in different stages of development (macules, papules, papulopustules) are present simultaneously. Preferred sites include the buttocks, hips, and axillae, particularly areas in contact with bathing suits; the palms and soles are generally spared. Otitis externa is also a common manifestation. Healing occurs spontaneously within 5 days, by drainage or regression. Rarely, scarring develops when a pustule progresses to furuncle formation. If folliculitis is acquired in a whirlpool, the lesions are sharply limited to the trunk below the upper part of the chest or neck. Inadequate chlorine levels in whirlpools, hot tubs, and swimming pools have been responsible for many of the outbreaks reported. In granulocytopenic and immunosuppressed hospitalized patients, *P. aeruginosa* O-11 from tap water used for washing was implicated in folliculitis that rapidly progressed to ecthyma gangrenosum.[36] Immersion is not required to develop *Pseudomonas* folliculitis; it has been reported in a toddler exposed to a contaminated washcloth and bath mat.[37] Folliculitis, often perioral and perinasal, caused by Enterobacteriaceae, can occur as a complication in patients with acne and rosacea, usually during prolonged courses of oral antibiotic therapy.[38] *P. aeruginosa* can also cause superinfection in patients with acne and rosacea after prolonged broad-spectrum antibiotic therapy.

Candida may cause folliculitis, typically producing pruritic satellite lesions surrounding areas of intertriginous candidiasis, commonly in infants or rarely in patients receiving prolonged antibiotic or corticosteroid therapy.[39] *Malassezia furfur,* a common skin saprophyte, or occasionally other dermatophytes, also produces a folliculitis with pruritic erythematous papules and papulopustules on the trunk, upper extremities, and face, particularly in the setting of diabetes mellitus, corticosteroid administration, or granulocytopenia,[39–41] and may be confused with acne vulgaris.[42] These lesions, particularly the early papulonodular ones, may suggest those of systemic candidiasis, a diagnosis that may seem to be supported by the presence of budding yeast forms on Gram-stained material from unroofed lesions. Unlike *Candida, M. furfur* requires lipid-supplemented media for primary isolation.

Additional nonbacterial folliculitis syndromes have been associated with herpes simplex, particularly in the presentation of severe sycosis barbae,[43] which may or may not be associated with secondary staphylococcal infection. Folliculitis, localized or disseminated, may occur after smallpox vaccination but does not represent progressive cutaneous viral infection.[44] Folliculitis has been associated with *Demodex* mite infestation[45] and rarely with parasitic disease.

Eosinophilic pustular folliculitis, a rare pruritic dermatosis characterized by recurrent crops of follicular papules and pustules with eosinophilic infiltration of perifollicular dermis, occurs particularly in the setting of acquired immunodeficiency syndrome (AIDS). It resembles bacterial or mycotic folliculitis but is a sterile process confirmed by biopsy.[46] Amicrobial pustulosis, another noninfectious folliculitis syndrome, may develop in normal hosts.[47] Folliculitis may develop after the use of tyrosine kinase inhibitors and immunomodulatory agents, including infliximab.[48]

Local measures such as saline compresses and topical antibacterial agents (e.g., mupirocin) or antifungal agents (e.g., clotrimazole) are usually sufficient to control the infection.[49] Severe or widespread disease (e.g., pseudomonal infection) may respond to oral fluoroquinolone therapy. Severe or refractory lesions should be cultured and considered for biopsy to assess uncommon causes of infection or noninfectious processes.

Furuncles and Carbuncles

Definition and Pathologic Characteristics

A furuncle (boil) is a deep inflammatory nodule extending into subcutaneous tissue that develops from preceding folliculitis. A carbuncle is a more extensive coalescent process involving multiple follicles that extends into the subcutaneous fat in areas covered by thick, inelastic skin. In the latter, multiple abscesses separated by connective tissue septa develop and drain to the surface along hair follicles.[21] *S. aureus* is almost invariably the causative agent (see Chapter 194), although occasionally coagulase-negative staphylococci can be recovered as the sole pathogen, particularly in elderly and immunocompromised patients.[50]

Clinical Manifestations

Furuncles occur in skin areas that are subject to friction and perspiration and contain hair follicles (especially the neck, face, axillae, and buttocks). Predisposing factors include obesity, blood dyscrasias, treatment with corticosteroids, defects in neutrophil function or number, and probably diabetes mellitus. MRSA as a cause of recurrent furunculosis is increasingly recognized.[51] A furuncle begins as a firm, tender, red nodule that soon becomes painful and fluctuant. Spontaneous drainage of pus commonly occurs, and the lesion subsides. A carbuncle is a larger, deeper, indurated, more serious lesion, usually located at the nape of the neck, on the back, or on the thighs. Fever and malaise are frequently

present, and some patients are acutely ill. As the lesion progresses, drainage occurs externally along the course of multiple hair follicles. A leukocytosis occurs, particularly if the lesion contains a large amount of undrained pus or if complicating cellulitis or bacteremia is present.

Bloodstream invasion can occur unpredictably (and is sometimes precipitated by manipulation of the lesions) and can result in endocarditis, osteomyelitis or other metastatic foci, and septic shock.[52] Lesions about the upper lip and nose present the special problem of possible spread of infection via the facial and angular emissary veins to the cavernous sinus.

Presumptive Therapy

Most furuncles are satisfactorily treated by the application of moist heat, which promotes localization and drainage of the process. Larger lesions may be drained to accelerate resolution. A carbuncle, a furuncle with surrounding cellulitis or fever, or a furuncle located about the midface generally requires systemic antibiotic therapy. Although conventional antistaphylococcal β-lactam antibiotics (e.g., dicloxacillin or cephalexin, 500 mg orally every 6–8 hours for an adult) are effective against MSSA, possible MRSA infection requires coverage with a suitable agent such as co-trimoxazole, often at generous dosage (e.g., 2 double-strength tablets twice daily). In a penicillin-allergic adult, clindamycin (300 mg orally every 6–8 hours), macrolides, or co-trimoxazole are alternatives, but in many communities there is significant resistance to macrolides and clindamycin. If the lesions are large and fluctuant, surgical drainage is indicated. Antibiotic treatment should be continued until evidence of acute inflammation has subsided. Patients with moderate to severe disease are best treated with initial parenteral therapy (e.g., vancomycin, linezolid, daptomycin, or ceftaroline; see Chapter 194).

Management of recurrent furunculosis presents a troublesome problem. This disease is not associated with a specific staphylococcal clonotype, although Panton-Valentine leukocidin expression appears to be a major virulence factor for the development of furuncles regardless of methicillin resistance status.[53] Most patients have no definable underlying defects in host defenses, although host abnormalities (e.g., granulocyte dysfunction, mannose-binding lectin deficiency) have been reported rarely[54,55]; *S. aureus* colonization (especially of the nares), recurrent skin trauma, and suboptimal hygiene are frequent contributing factors. Prophylaxis of recurrent episodes involves several measures:

1. *Antibiotic treatment.* Systemic antibiotic treatment as described should be administered for the most recent episode. Prolonged treatment (2 months) is no more effective than a 10- to 14-day course in preventing recurrences.
2. *General skin care.* Antibacterial soap and water should be used to reduce the number of *S. aureus* organisms on the body surface, and careful hand washing should be performed after contact with lesions. A separate towel and washcloth (carefully washed in hot water before reuse) should be reserved for the patient. Chlorhexidine solution (4%), an antimicrobial skin cleanser, hexachlorophene, or dilute bleach (0.005%; ½ cup in a 40-gallon tub)[56] may be used to decrease further staphylococcal skin colonization. Hexachlorophene is contraindicated for use in neonates and infants because of potential neurotoxicity.
3. *Care of clothing.* Sheets and underclothing should be laundered at high temperatures and changed daily.
4. *Care of dressings.* Draining lesions should be covered at all times with sterile dressings to prevent autoinoculation, and the dressings should be wrapped and promptly disposed of after removal.

Further measures aimed at elimination of nasal carriage and subsequent shedding of *S. aureus* (MSSA or MRSA) onto the skin may be warranted in the management of refractory cases. Intranasal application of a 2% mupirocin calcium ointment in a soft paraffin base twice daily for 5 days can eliminate short-term *S. aureus* carriage, with longer-term eradication success rates of approximately 60%.[57] Mupirocin resistance is very low in unselected community-acquired staphylococcal infections but may be substantial in selected populations.[58] Although oral rifampin has been used to eliminate staphylococcal nasal carriage and interrupt a cycle of recurrent furunculosis in selected patients, such monotherapy can lead to the rapid selection of rifampin-resistant strains. Intensive combined topical and systemic decolonization strategies (topical chlorhexidine, nasal mupirocin, and dual oral therapy with rifampin and doxycycline to prevent rifampin resistance) eradicated carriage in 74% of older adult patients colonized with MRSA.[58] Chlorhexidine resistance is uncommon but has been associated with the presence of staphylococcal plasmid-encoded efflux pumps and may contribute to decolonization failure.[59] Various staphylococcal vaccines have not proved effective in preventing recurrent furunculosis. Patients with recurrent furunculosis despite conventional treatment should undergo biopsy to assess possible uncommon pathogens; extensive furuncles caused by rapidly growing mycobacteria were identified in clients of a nail salon that had whirlpool footbaths.[60]

Ecthyma

The lesions of ecthyma begin in a fashion similar to those of impetigo but penetrate through the epidermis. Group A streptococci produce the lesions de novo or secondarily infect preexisting superficial lesions (e.g., insect bites, excoriations), with both mechanisms resulting in the same clinical picture.[61] Ecthyma lesions most frequently occur on the lower extremities, particularly in children and older adults. They consist of punched-out ulcers covered by greenish-yellow crusts that extend deeply into the dermis and are surrounded by raised violaceous margins. Treatment is the same as for impetigo. These group A streptococcal infections may lead to deeper parenchymal infection and also may trigger poststreptococcal glomerulonephritis.[61] Very extensive involvement with complicating bacteremia was reported in a patient with AIDS.[62] Invasive infections caused primarily by *P. aeruginosa* (ecthyma gangrenosum) may resemble streptococcal ecthyma initially but generally occur in compromised hosts and have a more aggressive course with frequent bacteremia (see later discussion); this pattern has been observed with a variety of pathogens and has sometimes developed in apparently normal hosts.[63]

Chancriform Lesions: Anthrax

A variety of infections, often with systemic consequences, are characterized by an initial chancriform lesion (see Table 93.1). Of the nonvenereal infections, anthrax has one of the most prominent chancriform lesions. (See Chapter 207 for a detailed discussion of anthrax.)

Pathogenesis

In the 20 years before 2001, naturally acquired anthrax infections, occurring in those working with raw imported wool, animal skins, and similar products contaminated with spores of *Bacillus anthracis,* were rare (<1 case/year) in the United States. Routine safety measures for such employees have almost eliminated anthrax from this group; sporadic cases still occur in transient workers in factories (e.g., ventilation repairmen) and in those who directly import wool for their own weaving. Most infections occur on the face, neck, or arms in an area with a minor abrasion. Anthrax has been associated with injection of heroin, particularly in the United Kingdom and other Western European countries, with characteristically deeper skin lesions.[64] Rarely, pulmonary infection occurs after inhalation of *B. anthracis* or intestinal anthrax results from ingestion of the organism (e.g., after playing animal-skin drums[65]). A bioterrorism-associated anthrax outbreak occurred suddenly in the United States in 2001, when *B. anthracis* spores were mailed in letters to Washington, DC, New York City, and Florida locations.[66] Twenty-two cases of anthrax ensued, 11 of the cutaneous form and 11 of the inhalational form.

Clinical Manifestations

After an incubation period of 1 to 8 days, a painless, sometimes pruritic, papule develops on an exposed area. The lesion enlarges, vesiculates (malignant pustule), and becomes surrounded by a wide zone of brawny, erythematous, gelatinous, nonpitting edema[67,68] as a result of local bacterial proliferation and toxin production.[69] The edema may become massive in young infants and in individuals with lesions on the face or neck and may suggest the diagnosis of cellulitis. Malaise and low-grade fever are present. As the lesion evolves, the initial vesicle enlarges and becomes hemorrhagic, necrotic, and covered by an eschar of variable

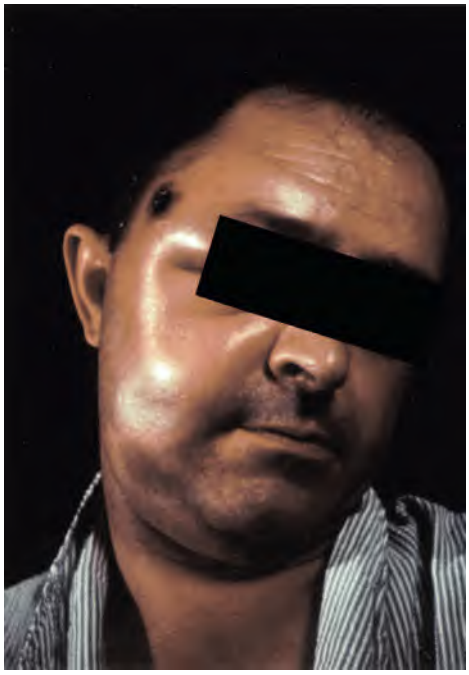

FIG. 93.2 Chancriform lesion of anthrax on the forehead. Note the prominent surrounding zone of gelatinous edema that is evident around the right eyelids. *(Courtesy Dr. Louis Weinstein, Boston.)*

TABLE 93.2 Initial Oral Antimicrobial Therapy for Cutaneous Anthrax When Risk of Bioterrorism Exists

DRUG	DOSAGE	DURATION
Adults		
Ciprofloxacin	500 mg q12h	60 days[b,c]
or		
Doxycycline	100 mg q12h	
Children		
Ciprofloxacin	15 mg/kg q12h (not to exceed 1 g/d)	60 days[b,c]
or		
Doxycycline[d]		
>8 yr and >45 kg	100 mg q12h	
>8 yr and ≤45 kg	2.2 mg/kg q12h	
≤8 yr	2.2 mg/kg q12h	

[a]See also Chapter 207.
[b]Previously, treatment recommended for cutaneous anthrax was for 7 to 10 days; this was increased to 60 days in the setting of bioterrorism risks because of the likelihood of concomitant aerosol exposure.
[c]Amoxicillin, 500 mg orally q8h for an adult (or 80 mg/kg/d, divided q8h, for a child), is an option for completion of treatment after clinical improvement.
[d]Use of tetracyclines is warranted in children because of the seriousness of the infection.
Modified from Centers for Disease Control and Prevention. Update: investigation of bioterrorism-related anthrax and interim guidelines for exposure management and antimicrobial therapy, October 2001. MMWR Morb Mortal Wkly Rep. *2001;50:909–919.*

dimensions (Fig. 93.2). Frequently, regional lymphadenopathy is present. Uncommonly, lymphangitis occurs from the initial process or from secondary infection. At all stages, the lesion remains painless. If untreated, bacteremic dissemination of infection from a skin site may occur, accompanied by high fever and hypotension. Meningitis may complicate bacteremic infection or primary pulmonary anthrax.

The epidemiologic background and the striking appearance of extensive gelatinous edema serve to distinguish anthrax from other types of chancriform lesions. A staphylococcal pustule or carbuncle with a necrotic eschar may be mistaken for early anthrax. However, the former is very painful and tender, and the causative agent can usually be demonstrated on a Gram-stained smear of material from the lesion. Other lesions mimicking the eschar of anthrax include ecthyma (usually lacking edema), ecthyma gangrenosum (usually in neutropenic patients with *P. aeruginosa* bacteremia), brown recluse spider bite (primarily in rural areas in southern and southwestern states and painful during incipient necrosis), orf (after exposure to sheep and with scab but without large eschar or gelatinous edema), and other infection-associated eschars at sites of tick or mite bites (e.g., from tularemia, rickettsial spotted fevers, scrub typhus).

Presumptive Therapy

Incision and débridement should be avoided because they may increase the likelihood of bacteremia, but skin punch biopsy after initiation of antimicrobial therapy may be necessary to establish the diagnosis by culture, immunohistochemical staining, or polymerase chain reaction (PCR) testing for *B. anthracis.* Almost all naturally occurring strains are susceptible to penicillin, and it has been the drug of choice for decades. With the concern that bioterrorism attack strains might be weaponized to be resistant to penicillins (and other commonly used antimicrobial agents), the initial treatment of cutaneous anthrax with oral ciprofloxacin or doxycycline has been recommended (Table 93.2).[70] Susceptibility studies of *B. anthracis* strains (both naturally occurring strains and those from the 2001 bioterrorism attacks) demonstrate susceptibility to ciprofloxacin, tetracyclines, clindamycin, imipenem, rifampin, chloramphenicol, aminoglycosides, cefazolin, vancomycin, macrolides, and linezolid. Obiltoxaximab, a monoclonal antibody directed against the protective antigen of *B. anthracis,* has been licensed as an adjunctive agent for the prophylaxis and therapy of inhalational anthrax.[71]

Erysipelas

Erysipelas is a distinctive type of superficial cellulitis of the skin, with prominent lymphatic involvement. It is generally attributed to infection by group A streptococci (uncommonly, by group C or G streptococci and rarely by group B streptococci, particularly in neonates, or *S. aureus*).[72] Admittedly, the causative pathogen is difficult to identify in nonbacteremic cases. Recent reviews of bacteremic patients with erysipelas recovered pathogens in 5% to 9% of cases, with 30% to 50% caused by group A streptococci, up to 40% due to other β-hemolytic streptococci, and roughly 10% to *S. aureus* or gram-negative pathogens.[73,74]

Clinical Manifestations

Erysipelas is more common in infants, young children, and older adults. Formerly, the face was most commonly involved, and an antecedent streptococcal respiratory tract infection preceded cutaneous involvement in about one-third of patients. Now, 70% to 80% of erysipelas lesions involve the lower extremities and 5% to 20% are on the face.[74,75] Portals of entry may be skin ulcers, local trauma or abrasions, psoriatic or eczematous lesions, or fungal infections, but often the skin of the involved area is grossly intact. In the neonate, erysipelas may develop from an infection of the umbilical stump. Predisposing factors include subclinical[76] or extensive lymphedema, venous stasis, obesity, paraparesis, diabetes mellitus, alcohol abuse, and nephrotic syndrome. Erysipelas tends to occur in areas of preexisting lymphatic obstruction or edema (e.g., after a radical mastectomy). In addition, because erysipelas itself produces lymphatic obstruction, it tends to recur in an area of earlier infection. Over a 3-year period, the recurrence rate is about 30%,[74,75] predominantly in individuals with venous insufficiency or lymphedema. Asymptomatic anal colonization with group A or G streptococci[77] or vaginal carriage of group B streptococci[78] may serve as a reservoir in individuals with relapsing erysipelas (or cellulitis).

Erysipelas is a painful lesion with a bright red, edematous, indurated (peau d'orange) appearance and an advancing, raised border that is sharply demarcated from the adjacent normal skin (Fig. 93.3). Fever is a feature. Facial erysipelas commonly extends across the bridge of the nose with bilateral involvement of the cheeks. Uncomplicated erysipelas remains confined primarily to the lymphatics and the dermis. Bullous erysipelas is a complication of severe disease that is observed in about

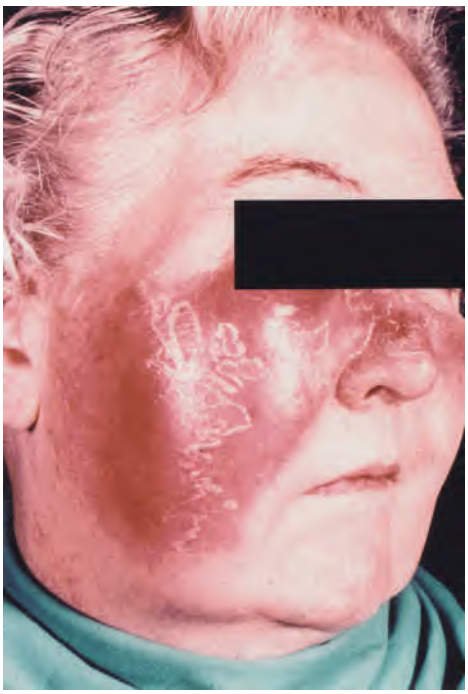

FIG. 93.3 Facial erysipelas involving both cheeks and bridge of nose. The sharp demarcation between the bright red area of erythema and the normal surrounding skin is evident. *(From Fitzpatrick TB, Eisen AZ, Wolff K, et al, eds.* Dermatology in General Medicine. *New York: McGraw-Hill; 1971.)*

5% of cases. The bullae are flaccid and intraepidermal, and cultures of blister fluid are often sterile before erosion occurs[79]; in some cases, *S. pyogenes* or *S. aureus* or both have been recovered, including MRSA strains.[80] Occasionally, the infection extends more deeply and produces cellulitis, subcutaneous abscess, and necrotizing fasciitis.

Leukocytosis is common. Group A streptococci usually cannot be cultured from the surface of the skin lesion, and only rarely can they be isolated from punch biopsy or tissue fluid aspirated from the advancing edge of the lesion. In cases of erysipelas complicating infected ulcers, group A and other β-hemolytic streptococci have been isolated from the ulcerated area in up to 30% of patients.

Differential Diagnosis

The diagnosis is made on the basis of the appearance of the lesion and the clinical setting. Early herpes zoster involving the second division of cranial nerve V may resemble unilateral facial erysipelas but can be distinguished by the pain and hyperesthesia preceding the skin lesions. Occasionally, contact dermatitis or giant urticaria may look like erysipelas but can be distinguished by the absence of fever and the presence of pruritus. Lesions closely resembling erysipelas, but apparently not caused by streptococcal infection, may occur repeatedly in patients with familial Mediterranean fever.[81] Diffuse inflammatory carcinoma of the breast may mimic low-grade erysipelas. Erythema chronicum migrans, the cutaneous lesion of Lyme disease, resembles erysipelas but is not painful, progresses much more slowly, may demonstrate central clearing, and has less associated fever. An erysipelas-like skin lesion was reported in several patients with hypogammaglobulinemia and *Campylobacter jejuni* bacteremia.[82]

Presumptive Therapy

Mild early cases of erysipelas in an adult may be treated with oral penicillin V (500 mg every 6 hours) or initial intramuscular procaine penicillin (600,000 units once or twice daily). Erythromycin (250–500 mg orally every 6 hours) or other macrolides are suitable alternatives in allergic patients; in some areas *S. pyogenes* demonstrates frequent macrolide resistance and clindamycin may be more appropriate, although clindamycin resistance among group A streptococci is rising (~15%).[83]

For more extensive erysipelas, patients should be hospitalized and receive parenteral aqueous penicillin G (2 million units every 6 hours), a first-generation cephalosporin, or ampicillin-sulbactam therapy. Although typical erysipelas can be readily distinguished from cellulitis, which can be of staphylococcal or streptococcal origin, the differentiation occasionally may not be clear-cut. Under such conditions, antistaphylococcal therapy (nafcillin, oxacillin, ampicillin-sulbactam, or a first-generation cephalosporin) should be considered. In an acutely ill patient or a patient with significant bullous erysipelas, intravenous administration of vancomycin is indicated to treat possible MRSA[80] or nonsusceptible streptococci pending blood culture results. Chronic antibiotic suppression (oral penicillin or parenteral benzathine penicillin) may reduce the recurrence rate of erysipelas or lower extremity cellulitis.[84–86]

Cellulitis

Cellulitis is an acute spreading infection of the skin that extends deeper than erysipelas and involves the subcutaneous tissues. Group A streptococcus, other β-hemolytic streptococci, and *S. aureus* are the most common causative agents.

Clinical Manifestations

Previous trauma (laceration, abrasion, puncture wound), often minor (shaving or athletic abrasion), or an underlying skin lesion (furuncle, ulcer, dermatophyte infection) predisposes to the development of cellulitis. Occasionally, secondary cellulitis results from bloodborne spread of infection to the skin and subcutaneous tissues; rarely, it is caused by direct spread from subjacent infections (subcutaneous abscesses, fistulas from osteomyelitis). Within several days after the inciting trauma, local tenderness, pain, and erythema develop and rapidly intensify. Malaise, fever, and chills develop. The involved area is often extensive, with marked erythema, warmth, and swelling. In contrast to erysipelas, the borders of a cellulitic area are not elevated and sharply demarcated; patchy involvement with skip areas may occur. Regional lymphadenopathy is common, lymphangitic streaking proximal to the cellulitic area is occasionally present, and bacteremia can occur. Local abscesses may develop, and small patches of overlying skin may subsequently undergo necrosis. A nidus of suppuration with surrounding cellulitis is a hallmark of staphylococcal cellulitis, although this diagnostic finding is not always present. Superinfection with gram-negative bacilli may supervene.

Cellulitis caused by group A streptococci may occur as a postoperative wound infection. Although it is uncommon today, it is particularly noteworthy because of the rapidity with which it can spread and invade the bloodstream. Such infection may be manifested within 6 to 48 hours after surgery (comparable to the short incubation period of postoperative clostridial myonecrosis), earlier than the usual postoperative staphylococcal infection, which is not evident for at least several days after surgery. Hypotension, often associated with bacteremia, may be the initial sign of infection, before significant incisional erythema is evident. A thin serous discharge may be expressed on compression of the wound margins, and streptococci can be identified on a Gram-stained smear.

Cellulitis is a serious disease because of the propensity of infection to spread via the lymphatics and bloodstream. Cellulitis of the lower extremities, particularly in older patients, may be complicated by thrombophlebitis. In patients with chronic dependent edema, cellulitis may spread extremely rapidly.

A form of cellulitis that is distinctive by virtue of its clinical setting occurs in the lower extremities of patients whose saphenous veins have been harvested for coronary artery bypass surgery.[87] Occasionally, an associated lymphangitis is present. In some patients, episodes of cellulitis are recurrent. Systemic manifestations such as chills, high fever, and toxicity are prominent. The area of cellulitis extends along the course of the saphenous venectomy, with marked edema, erythema, and tenderness. Occasionally, the involved areas are somewhat similar to those observed in erysipelas (pseudoerysipelas). Although a bacterial cause is not defined in most cases, isolates available from involved skin or blood implicate non–group A β-hemolytic streptococci (groups C, G, and B) as major causes. The portal of entry of the infection is often an associated area of tinea pedis. The combination of compromised lymphatic drainage and minor venous insufficiency after saphenous venectomy may result in lower leg edema, a favorable setting for cellulitis. Endoscopic

TABLE 93.3 Anatomic Variants of or Predispositions to Cellulitis

ANATOMIC VARIANT OR PREDISPOSITION	LOCATION	LIKELY BACTERIAL CAUSE
Periorbital cellulitis	Periorbital	*Staphylococcus aureus, Streptococcus pneumoniae,* group A streptococci
Buccal cellulitis	Cheek	*Haemophilus influenzae* type b
Cellulitis complicating body piercing	Ear, nose, umbilicus	*S. aureus,* group A streptococci
After mastectomy (with axillary node dissection)[77]	Ipsilateral upper extremity	Non–group A β-hemolytic streptococci
After lumpectomy (with limited axillary node dissection, breast irradiation)[78]	Ipsilateral breast	Non–group A β-hemolytic streptococci
After saphenous vein harvest for coronary artery bypass	Ipsilateral leg	Group A or non–group A β-hemolytic streptococci
After radical pelvic surgery, radiation therapy	Vulva, inguinal areas, legs	Group B and group G streptococci
After liposuction	Thigh, abdominal wall	Group A streptococci, peptostreptococci
Postoperative (very early) wound infection	Abdomen, chest, hip	Group A streptococci
Injection drug use ("skin popping")	Extremities, neck	*S. aureus,* streptococci (groups A, C, F, G)[a]
Perianal cellulitis	Perineum	Group A streptococcus

[a]Other bacteria to consider based on isolation from skin or abscesses in this setting include *Enterococcus faecalis,* viridans-group streptococci, coagulase-negative staphylococci, anaerobes (including *Bacteroides* and *Clostridium* spp.), and Enterobacteriaceae.

venous harvesting appears to have a lower risk for postoperative lower extremity cellulitis than open venectomy.[88,89] The inflammation from an initial episode of cellulitis, erysipelas, or lymphangitis obstructs lymphatic drainage, enhancing the predisposition to further episodes of infection. Other variants of postoperative cellulitis or predispositions to cellulitis have been described (Table 93.3).[90–92]

Recurrent cellulitis is a common and vexing problem and has been observed in 22% to 49% of patients with cellulitis.[93,94] A variety of predisposing local factors have been reported, including chronic edema, lymphedema, venous insufficiency, deep venous thrombosis, peripheral vascular disease, tinea pedis, and saphenous vein surgery, as well as obesity, which contributes to venous stasis and lymphedema.[93,95] In addition to providing increased quantities of interstitial protein-rich fluid, lymphedema affects immune cell trafficking and innate immune processes, which may contribute to the risk of recurrent cellulitis.[96,97] Microsurgical lymphovenous anastomosis has been studied to diminish lymphedema and appears to reduce the rate of recurrent cellulitis.[98] Recurrent episodes of cellulitis or pseudoerysipelas caused by groups B and G streptococci have also occurred in patients with lower extremity lymphedema secondary to radical pelvic surgery, radiation therapy, or neoplastic involvement of pelvic lymph nodes.[90] Typically, the cellulitis involves the vulva, inguinal areas, and both lower extremities. In this setting, recurrent episodes have occurred in association with recent coitus.[99] An uncommon but distinctive form of streptococcal cellulitis, perianal group A streptococcal cellulitis, occurs principally in children.[100,101] The clinical features consist of perianal pruritus, purulent secretions, intense perianal erythema, pain on defecation, blood-streaked stools from anal fissures, and chronicity (months) if not treated with penicillin. Relapse is relatively common because perianal colonization often persists despite appropriate systemic oral therapy and eradication attempts with clindamycin or rifampin are not consistently effective.

Depending on the clinical setting, cellulitis caused by a number of nonstreptococcal pathogens may be seen.[102] Before routine immunization of infants with the conjugated protein polysaccharide *Haemophilus influenzae* type b vaccine, buccal cellulitis—originating in the upper respiratory tract, often demonstrating a bluish (blue dome) appearance, and caused by *H. influenzae* type b—accounted for up to 25% of cases of facial cellulitis in infants in the 3- to 24-month age group.[102] Complicating bacteremia was frequently present. Rarely, pneumococcal facial cellulitis acquired through the bacteremic route presents in children[103] and in adults with a variety of underlying systemic risk factors.[104] Soft tissue infections by the pneumococcus can bear a striking resemblance to streptococcal erysipelas. A rare but particularly troublesome, chronic, and progressive form of cellulitis, known as dissecting cellulitis of the scalp or perifolliculitis capitis, is probably similar to hidradenitis suppurativa and acne conglobata in pathogenesis, and often occurs in conjunction with these inflammatory disorders.[105] The clinical features consist of recurrent painful, fluctuant dermal and subcutaneous nodules accompanied by purulent drainage from burrowing interconnecting abscesses, scarring, and alopecia. *S. aureus* is most commonly isolated. Effective treatment has involved wide excision and skin grafting. A variety of antiinflammatory regimens, including isotretinoin, dapsone, and infliximab, have been reported to be successful in case reports in the literature.

A polymorphonuclear leukocytosis is usually present, regardless of the bacterial cause of cellulitis. Although culture of needle aspirates from areas of cellulitis is not indicated ordinarily because of generally low sensitivity rates, such studies provide the best information on likely pathogens,[106] as noted in a recent systematic review demonstrating that such direct sampling identified a pathogen in only 16% of 808 patients. Together, *S. aureus* (~50%) and group A streptococci (~25%) represented over 75% of recovered pathogens. The remaining identified pathogens included group B and viridans-group streptococci, *Enterococcus faecalis,* gram-negative bacilli (Enterobacteriaceae, *H. influenzae, Pasteurella multocida, P. aeruginosa,* and *Acinetobacter* spp.), and rarely *Candida albicans.*[106] Cultures of ulcers and abrasions contiguous with areas of cellulitis have shown similar gram-positive pathogens (*S. aureus* or group A streptococci, or both). It is reasonable to consider diagnostic aspiration only if unusual pathogens are suspected (e.g., in immunocompromised patients), fluctuant areas are detected, or initial antimicrobial therapy has been unsuccessful.

A broader spectrum of pathogens has been isolated from deep wounds or débrided tissue in diabetic patients with limb-threatening infections (including cellulitis).[107] These include gram-positive aerobes in the majority of patients (*S. aureus,* including methicillin-resistant *S. aureus; Enterococcus* spp.; various streptococcal species), with common recovery as well of both gram-negative aerobes (Enterobacteriaceae, *Acinetobacter, P. aeruginosa*) and anaerobes (*Bacteroides, Peptococcus*). In cellulitis complicating decubitus ulcers, this broad range of microorganisms also should be considered as potential pathogens. If this complication develops in a hospitalized patient, resistant nosocomial pathogens should be considered when deciding on empirical antibiotic coverage.[107] *Helicobacter cinaedi* cellulitis and bacteremia have been reported in immunocompetent patients recovering from orthopedic surgery[108] and in immunocompromised hosts.[109]

Blood cultures are positive in only 2% to 8% of patients with community-acquired cellulitis,[73,93] although, recently, positive blood cultures were reported in 18.4% of patients in a large prospective multicenter analysis conducted in Spain.[94] Roughly three-fourths of isolates are group A or other β-hemolytic streptococci (particularly group C or G), or *S. aureus,* and the remainder are diverse gram-negative pathogens, including *H. influenzae, P. multocida, P. aeruginosa,* Enterobacteriaceae, or *Vibrio vulnificus.* Blood cultures appear to be positive more frequently with cellulitis superimposed on lymphedema.[110]

Environmental exposures are often important risk factors for the development of cellulitis. *Erysipelothrix rhusiopathiae* is the causative agent of erysipeloid, a somewhat indolent cellulitis occurring principally in persons who handle saltwater fish, shellfish, poultry, meat, and hides[111] (see Chapter 209). The infection, which usually occurs in the summer,

is introduced through an abrasion on the hands. A painful violaceous area appears within 1 week after the injury. As the process spreads peripherally with distinct raised borders, the central portion of the lesion clears. Ulceration is not a feature. Occasionally, an adjacent joint is involved; rarely, bacteremia and endocarditis may follow. The causative organism is not usually observed in Gram-stained drainage from the lesion but may be isolated on culture of a biopsy specimen taken from the advancing margin of the lesion. The development of a typical lesion in a person handling fish or meat products suggests the diagnosis. Other forms of bacterial cellulitis or erysipelas may resemble erysipeloid, particularly if the lesion is on the hand and evolves gradually. A somewhat similar lesion of unknown origin, called seal finger, occurs in aquarium workers and veterinarians secondary to seal bites or trauma sustained in caring for these animals. Although penicillin is the antibiotic of choice for the treatment of erysipeloid, it appears that seal finger responds to tetracycline.[112] In support of this practice, a novel *Mycoplasma* species has been identified by 16S ribosomal RNA PCR from a patient with seal finger and subsequent disseminated infection.[113] *Aeromonas hydrophila,* a gram-negative bacillus found particularly in lakes, rivers, and soil, may produce an acute cellulitis after introduction of the organism through a laceration acquired during swimming in fresh water. These infections occur most often in spring and summer.[114,115]

Cellulitis, bullous lesions, or necrotic ulcers may complicate infection of a traumatic wound sustained in salt water (or brackish inland waters)[116] or from contact with raw seafood. Such infections, caused by *Vibrio* species (primarily *V. vulnificus* but also occasionally *Vibrio alginolyticus,* non–serogroup O1 *Vibrio cholerae,* and *Vibrio parahaemolyticus*),[115] can result in bacteremia and progress to necrosis, which requires extensive surgical débridement.[117] A rapidly progressive primary septicemia caused by *V. vulnificus* may occur after entry of the organism through the gastrointestinal tract (e.g., consumption of raw oysters) rather than through abraded skin. Cellulitis with hemorrhagic skin bullae often occurs rapidly after the bacteremia. Particularly at risk for the septicemic form of disease are patients with alcoholic cirrhosis, hemochromatosis, or thalassemia—presumably as a result of enhanced growth of *V. vulnificus* mediated by these processes associated with enhanced iron storage. The systemic *Vibrio* infections have mortality rates of 20% to 40%.[118,119] These vibrios are generally susceptible in vitro to tetracyclines, chloramphenicol, aminoglycosides, and third-generation cephalosporins. Tetracyclines have been considered first-line treatment of *V. vulnificus* infections, with cefotaxime and ciprofloxacin as alternatives.[102] Combination therapy with doxycycline and a third-generation cephalosporin is frequently recommended.[115] A variety of bacteria (*Serratia, Proteus,* other Enterobacteriaceae, *Campylobacter* [both *C. fetus* and *C. jejuni*], and *H. cinaedi*[120]) and fungi (*Cryptococcus neoformans,*[121] *Fusarium* spp.[122]) that rarely cause cellulitis in healthy individuals may produce bloodborne cellulitis in an immunocompromised or granulocytopenic patient. *Legionella* species have very rarely produced cellulitis (*L. pneumophila* in association with pneumonia[123] and *L. micdadei* in a renal transplant recipient[124]). Spontaneous *Escherichia coli* cellulitis occurs in children with symptomatic nephrotic syndrome[125] and in neutropenic patients with underlying hematologic malignancy, often with accompanying septic shock.[126]

A variety of processes that resemble cellulitis in appearance should be distinguished from it.[93,127,128] These include infections as well as inflammatory and neoplastic entities (Table 93.4).

Envenomation after puncture wounds by the spines of a stonefish (indigenous to shallow waters of the South Pacific) produces local edema and erythema that may suggest acute bacterial cellulitis acquired in seawater.[129] This reaction may be accompanied by serious systemic toxicity, including acute pulmonary edema. Numerous other marine species can provoke cutaneous reactions with prominent vesicular formation or urticaria that may mimic cutaneous infection.[130]

Familial Mediterranean fever is seen in Sephardic Jews and in those from the Middle East. Patients have a history of previous bouts of fever, sometimes accompanied by erysipelas- or cellulitis-like, noninfectious episodes of localized erythema and often by crises of abdominal pain.[81,131]

Sweet syndrome consists of the acute development of tender erythematous pseudovesiculated plaques, fever, and neutrophilic leukocytosis, often associated with malignancy or a variety of medications.[132,133] If lesions occur on the face, they may suggest erysipelas or periorbital cellulitis.[134]

Kawasaki disease occurs in infancy or childhood and is characterized by fever, conjunctivitis, acute cervical lymphadenopathy, and a polymorphic eruption. Facial rash and conjunctivitis may suggest periorbital cellulitis,[135] and trunk and especially perineal involvement may suggest cellulitis. The constellation of clinical and laboratory findings typically supports the diagnosis of Kawasaki disease.

The appearance and clinical features of Wells syndrome (eosinophilic cellulitis) consist of urticaria-like, moderately erythematous, edematous lesions that develop rapidly and are often accompanied by fever. It can be distinguished from the usual bacterial cellulitis by its minimal tenderness, lack of local heat, and failure to respond to antibiotics. Biopsy of the early lesion shows marked infiltration of the dermis with eosinophils. The lesions resolve in several weeks but frequently recur and respond to corticosteroid therapy.[136] A variety of empirical therapies have been employed, but randomized clinical trials are lacking.[137]

Lymphatic cutaneous metastases from neoplasms, particularly adenocarcinoma, may produce a localized, edematous, erythematous lesion resembling cellulitis. First described as inflammatory carcinoma of the breast, carcinoma erysipeloides involves the skin overlying the site of the primary tumor or at sites of distant metastases. Progression is slower than that of cellulitis, and fever is not a feature.[138] Very rarely, lymphomatous involvement of subpectoral or retromammary nodes may produce an erythematous lymphedema of the breast, suggesting subacute cellulitis or inflammatory carcinoma of the breast.

TABLE 93.4 Infectious and Noninfectious Processes to Be Distinguished From Cellulitis

Infections
Herpes simplex
Herpes zoster
Necrotizing fasciitis types I and II
Anaerobic myonecrosis (gas gangrene)
Cutaneous anthrax with prominent surrounding gelatinous edema
Prominent response to vaccination with vaccinia
Erythema chronicum migrans lesion of Lyme disease
Inflammatory and Neoplastic Processes
Hematoma
Venous stasis dermatitis
Calciphylaxis
Insect bite (hypersensitivity response)
Fixed drug reaction
Envenomation from spines of stonefish
Acute gout
Deep venous thrombophlebitis of lower extremity
Familial Mediterranean fever–associated cellulitis-like erythema
Pyoderma gangrenosa (particularly lesions starting in subcutaneous fat as acute panniculitis)
Sweet syndrome (acute febrile neutrophilic dermatosis)
Kawasaki disease
Wells syndrome (eosinophilic cellulitis/fasciitis)
Carcinoma erysipeloides

Modified from Swartz MN. Clinical practice: cellulitis. N Engl J Med. *2004;350:904–912. Copyright ©2004 Massachusetts Medical Society.*

Presumptive Therapy

Concern regarding MRSA infection has complicated routine empirical cellulitis therapy.[21,93,139,140] Traditionally, β-lactam antibiotics active against penicillinase-producing *S. aureus* were administered for the initial treatment of cellulitis because the great majority of cases were caused by streptococci or MSSA; cephalosporins were sometimes used for lower extremity infection, particularly when comorbid conditions (diabetes mellitus, peripheral vascular disease) or trauma was present. Streptococcal cellulitis typically has a more acute presentation and progression than staphylococcal disease, and β-lactam therapy can be initiated in this setting. More indolent cellulitis or infection associated with a focal abscess, pustule, or eschar is more suggestive of staphylococcal disease and should be addressed initially with therapy effective against MRSA.[141] The Infectious Diseases Society of America practice guidelines distinguish

between purulent and nonpurulent cellulitis; empirical therapy for the former should be targeted toward MRSA, whereas empirical therapy for the latter may still include a penicillinase-resistant β-lactam to treat hemolytic streptococci and MSSA.[140] After initiating empirical therapy, it is crucial to monitor patients closely and to revise therapy if there is a poor response to initial treatment.

Intravenous antibiotic therapy is essential if the lesion is rapidly spreading, the systemic response is prominent, or there are significant comorbidities (i.e., asplenia, neutropenia, immunocompromise, cirrhosis, cardiac or renal failure, local trauma, or preexisting edema). Cefazolin (1.0–1.5 g IV every 8 hours) or nafcillin (2.0 g IV every 4–6 hours) is a reasonable choice for an average-risk adult with moderately severe nonpurulent cellulitis. When addressing severe cellulitis or moderate disease in high-risk individuals as well as in penicillin-allergic individuals, vancomycin (1.0 g IV every 12 hours) or linezolid (0.6 g IV every 12 hours) is indicated. Once-daily intravenously administered daptomycin is also an option for treatment of MRSA staphylococcal soft tissue infections; the "fifth-generation" cephalosporin ceftaroline may evolve to become a more common, cost-effective second-line therapy against MRSA skin infections.[142] Several newly approved agents with broad activity against gram-positive pathogens and unique pharmacokinetic features are also available, including the lipoglycopeptide agents dalbavancin, telavancin, and oritavancin, and the second-generation oxazolidinone agent tedizolid. Their cost-effective role in the management of patients with cellulitis and other skin infections is not established.[143] After nafcillin therapy for nonpurulent cellulitis, dicloxacillin or cephalexin (0.5 g every 6–8 hours) or a longer-acting agent (e.g., cefadroxil 0.5–1.0 g once or twice daily) may be given once fever abates and skin lesions begin to resolve. Follow-up oral therapy for adult patients with MRSA infection requires linezolid (0.6 g every 12 hours); clindamycin may be used if MRSA is recovered from purulent material and sensitivity is confirmed in vitro.

In many communities, MRSA isolates have significant rates of clindamycin resistance. If the cellulitis is early and mild and no significant comorbidities are present, initial therapy with the previously noted oral follow-up antimicrobial agents may be used initially. Although co-trimoxazole is not approved by the US Food and Drug Administration for the treatment of MRSA skin and soft tissue infections, it is widely utilized to treat proven and presumed staphylococcal (especially MRSA) skin infections.[144] A recent prospective trial assessing the benefit of oral co-trimoxazole in addition to cephalexin for the treatment of outpatient cellulitis showed no added benefit, presumably reflecting the paucity of MRSA as the etiology of these infections.[145] A recently conducted study investigated treatment of 524 patients with cellulitis or skin abscesses or both, treated with either clindamycin or co-trimoxazole. The proportion of patients cured was similar in both groups (in evaluable patients, 89.5% in the clindamycin group and 88.2% in the co-trimoxazole group),[146] although the incidence of clindamycin resistance among the methicillin-resistant staphylococcal isolates was low (4.5%). The comparability of these agents might possibly differ in areas where there is a significantly higher rate of resistance to either agent. There were nonsignificant differences favoring co-trimoxazole in patients who had abscesses, and favoring clindamycin in those who had only cellulitis.[147] A recently conducted study compared treatment of uncomplicated skin abscesses undergoing drainage with supplemental trimethoprim-sulfamethoxazole (320/1600 mg twice daily) for 7 days or placebo, and achieved clinical cure of abscesses in 80.5% of trimethoprim-sulfamethoxazole recipients compared with 73.6% of placebo recipients ($P < .001$).[148] The majority of isolates that were obtained were MRSA (43.5%) or MSSA (15.9%).

Cellulitis in the setting of a diabetic foot infection may involve a much wider spectrum of potential pathogens and warrants broader antimicrobial coverage, such as ampicillin-sulbactam (3.0 g IV every 6 hours in adults), imipenem-cilastatin or meropenem, or other antimicrobial combinations targeting anaerobes as well as gram-positive and gram-negative aerobes.[107] Vancomycin coverage against MRSA is frequently administered as well, particularly in patients who have had prior MRSA infection, reside in areas of high MRSA incidence, or have severe infection.[107]

Specially tailored initial antimicrobial therapy is warranted if additional bacterial species are likely to be involved in cellulitis after unusual exposures. These include human or animal bites, for which initial therapy might involve ampicillin-sulbactam given intravenously or amoxicillin-clavulanate orally (500 mg every 8 hours or 875 mg every 12 hours in an adult). In the setting of cellulitis after an abrasion or laceration occurring with saltwater exposure, in which *V. vulnificus* might be the pathogen, treatment with doxycycline (200 mg IV daily in two divided doses) along with an antimicrobial agent targeted to pathogens that are more common is appropriate. Similarly, in the setting of cellulitis after an abrasion or laceration occurring with freshwater exposure, in which *A. hydrophila* might be involved, initial treatment with ciprofloxacin (400 mg IV or 500 mg orally every 12 hours) along with an antimicrobial agent targeted to more common pathogens is indicated; alternatively, a combination of ceftazidime plus gentamicin may be used.

Initial local care of cellulitis includes immobilization and elevation of the involved limb to reduce swelling and application of a cool, sterile saline dressing to remove purulent exudate from any associated ulcer or infected abrasion and to decrease local pain. Patients who have cellulitis at the saphenous site after coronary artery bypass surgery and fungal infection in the interdigital spaces should be treated topically for the latter with miconazole, clotrimazole, or terbinafine. The initial antibiotic (e.g., cefazolin) should be given by the intravenous route for 3 to 5 days, until fever abates and skin findings begin to resolve, to ensure prompt resolution before switching to other routes of therapy. Attention to the problem of tinea pedis before bypass surgery can prevent this form of cellulitis. Similar prompt attention to pedal epidermophytosis in patients who have had one such episode of cellulitis can obviate subsequent episodes.

Recurrent episodes of cellulitis usually occur in patients with peripheral edema. The use of support stockings and good skin hygiene can reduce its frequency or eliminate recurrences. Patients with lymphedema may benefit from regular lymphatic pneumatic compression treatments to improve chronic lymphedema and reduce the frequency of recurrent infections.[149] In the occasional patient who continues to have frequent episodes of cellulitis or erysipelas despite such measures, prophylactic monthly benzathine penicillin, oral penicillin V (250–500 mg twice daily),[85,86,150] or erythromycin (250 mg orally once or twice daily) for the penicillin-allergic patient may be indicated.[21]

Membranous Ulcers

Infected ulcers of varied or mixed bacterial origin may be covered at their base by a layer of necrotic debris resembling a membrane. The latter is not usually strongly adherent and can be removed without much difficulty. In addition, such a lesion generally has abundant purulent drainage, attributable to infection with pyogenic bacteria. Membrane-covered lesions (both superficial and deep ulcers) are also produced by cutaneous infection with *Corynebacterium diphtheriae* (see next section).

Cutaneous Diphtheria

Cutaneous diphtheria (see Chapter 204) is uncommon in developed countries; most cases occur in unimmunized persons in overcrowded, underdeveloped parts of the world (particularly in tropical areas), in republics of the former Soviet Union, and among refugee populations[151,152] and are associated with skin trauma, including insect bites, poor hygiene, and inadequate immunization. Endemic toxigenic *C. diphtheriae* has been documented among Northern Plains Native Americans and among the urban destitute in Vancouver, British Columbia.[153] In addition, cutaneous diphtheria has been imported by travelers returning from areas of endemic diphtheria, including the republics of the former Soviet Union. Toxigenic *Corynebacterium ulcerans* can also produce cutaneous diphtheria,[154] and its incidence is rising in much of Western Europe.

Clinical Manifestations

Three types of cutaneous lesions have been described in cutaneous diphtheria: (1) wound diphtheria—secondary *C. diphtheriae* infection of a preexisting wound, which becomes partially covered by a membrane and encircled by a zone of erythema; (2) primary cutaneous diphtheria—a disease of the tropics that begins as a single pustule or as several pustules, usually on a lower extremity, and progresses to form a punched-out ulcer covered by a gray-brown membrane; and (3) superinfection of

eczematized skin lesions—a superficial membranous infection. *C. diphtheriae* has also been isolated from lesions resembling impetigo, ecthyma, and infected insect bites, where they may represent true infections or merely a cutaneous carrier state.[155] Chronic, nonhealing skin ulcers in intravenous drug users that are caused by trauma and are infected with *S. aureus* or various types of streptococci have been found on occasion to be superinfected with nontoxigenic strains of *C. diphtheriae*.[156] Cutaneous diphtheria may be as contagious as the respiratory form of the disease among schoolchildren.

Occasionally, membranous pharyngitis accompanies cutaneous diphtheria. However, 20% to 40% of patients with cutaneous diphtheria carry *C. diphtheriae* in their upper respiratory tract.[155] Myocarditis is extremely rare as a complication of cutaneous diphtheria, but cranial nerve palsies and Guillain-Barré syndrome occur in 3% to 5% of patients with membranous diphtheritic skin ulcers.

Laboratory Findings

Characteristic beaded, metachromatically staining bacilli can be found in methylene blue–stained smears of the edge of the membrane, but the diagnosis can be established only by isolation of *C. diphtheriae* from a suggestive skin lesion. Selective media (cystine tellurite blood agar or fresh Tinsdale medium) are necessary for isolation to inhibit other bacteria in skin ulcers; a specific request for *C. diphtheriae* culture generally is required. Rapid speciation by mass spectroscopy is performed in reference laboratories. In addition to isolation of the organism, toxigenicity should be demonstrated by an Elek plate (agar diffusion precipitin reaction), by diphtherial toxin gene analysis by PCR assay, or by guinea pig inoculation (dermonecrosis).[157]

Differential Diagnosis

Pyogenic infection of ulcerated traumatic lesions is usually purulent, and the lesions are not covered by a membrane. Cutaneous fungal infections have more proliferative and irregular margins. The early stages of primary cutaneous diphtheria and secondary infection of insect bites and abrasions with *C. diphtheriae* may closely resemble those of impetigo. Cutaneous diphtheria may be misdiagnosed as pyoderma gangrenosum.

Presumptive Therapy

If a presumptive diagnosis of ulcerative cutaneous diphtheria is made on clinical grounds and on the basis of preliminary bacteriologic findings, antitoxin (20,000–40,000 units IM or IV) is administered after testing for sensitivity to horse serum. Antibiotic administration (erythromycin, 2.0 g/day orally; or procaine penicillin, 1.2–2.4 million units/day IM for 7–10 days in an adult) also assists in elimination of the convalescent carrier state. Removal of necrotic debris aids in healing of the lesions.

Infectious Gangrene (Gangrenous Cellulitis)

Infectious gangrene is a rapidly progressive cellulitis with extensive necrosis of subcutaneous tissues and the overlying skin. Several clinically distinct syndromes are recognized, depending on the specific causative organism, anatomic location of the infection, and predisposing conditions. Such clinical entities include the following:

1. Necrotizing fasciitis: type I, or polymicrobial, often including Enterobacteriaceae and anaerobes; type II, or streptococcal gangrene caused by *S. pyogenes*; type III, caused by *Vibrio* or other marine pathogens
2. Gas gangrene (clostridial myonecrosis) and anaerobic cellulitis
3. Progressive bacterial synergistic gangrene
4. Synergistic necrotizing cellulitis, perineal phlegmon, and gangrenous balanitis
5. Gangrenous cellulitis in an immunosuppressed patient
6. Very localized areas of skin necrosis complicating conventional cellulitis

Pathologic Characteristics and Pathogenesis

The pathologic changes of gangrenous cellulitis are those of necrosis and some hemorrhage in the skin and subcutaneous tissues. In most types of gangrenous cellulitis, an abundant polymorphonuclear leukocytic exudate is present, but in clostridial myonecrosis, the exudate is thin and consists of fluid, fibrin, and gas but few leukocytes. Fibrin thrombi are frequently present in small arteries and veins of the dermis and subcutaneous fat, particularly in streptococcal gangrene.[158] In most cases, gangrenous cellulitis develops after introduction of the infecting organism at the infected site. It may also result from extension of infection from a deeper focus to involve the subcutaneous tissues and skin, as in clostridial myonecrosis after intestinal surgery or in perineal phlegmon after dissection of infection from a perirectal abscess. Occasionally, gangrenous cellulitis begins at a site of metastatic infection in the course of a bacteremia (e.g., clostridial myonecrosis caused by *Clostridium septicum* at a peripheral site secondary to spread from an associated colonic neoplasm, or *Pseudomonas* gangrenous cellulitis).

Clinical Manifestations

Streptococcal gangrene. Streptococcal gangrene is a rare form of cutaneous and subcutaneous gangrene caused by group A (or C or G) streptococci, involving the superficial fascia but generally sparing the deep fascial (muscle fascia) layer, that usually develops at a site of trauma on an extremity but may occur in the absence of an obvious portal of entry. Like necrotizing fasciitis type II (see "Necrotizing Fasciitis" later), surgical exploration and thorough débridement are critical. The lesion begins as a local, exquisitely painful area of erythema and edema. The extent of this aggressive process initially is often underestimated, because it spreads widely in the deep subcutaneous tissue, with relative sparing of overlying skin.[159] The streptococcal toxic shock syndrome may evolve rapidly and be the most prominent feature.[160] If untreated, the skin becomes dusky over the next 1 to 3 days. Bullae containing yellowish to red-black fluid develop and rupture.[161] The lesion evolves into a sharply demarcated area covered by necrotic eschar and surrounded by a border of erythema. The process at this point resembles a third-degree burn, for which it could be mistaken if a history were not available. Lymphangitis is rarely evident. Extensive necrotic sloughing can result because of deep penetration of the infection along fascial planes. Bacteremia, metastatic abscesses, and death may result from this life-threatening illness if appropriate combined antibiotic therapy and surgical exploration are not initiated promptly. Secondary thrombophlebitis may be a complication if the lower extremities are involved. Streptococci can usually be cultured from the early bullous lesions and frequently from blood.

Progressive bacterial synergistic gangrene. This distinctive lesion usually occurs after infection at an abdominal operative wound site (frequently when wire sutures have been used) or abutting an ileostomy or colostomy, a fistulous tract, or a chronic ulcer on an extremity.[162] It begins as a local tender area of swelling and erythema that subsequently ulcerates. The painful shaggy ulcer gradually enlarges and is characteristically encircled by a margin of gangrenous skin (Fig. 93.4). Surrounding the latter is a violaceous zone that fades into an outer, pink, edematous border area. If untreated, the process extends slowly but relentlessly, ultimately producing an enormous ulceration.

Microaerophilic or anaerobic streptococci can be recovered from aspirates of the advancing margin of the lesion, and *S. aureus* (or occasionally *Proteus* or other gram-negative bacilli) are present in the ulcerated area. Meleney[162] reproduced similar lesions by experimentally injecting both microaerophilic streptococci and *S. aureus* (but not either alone) into the skin of animals. Similar lesions can be seen rarely with amebic (*Entamoeba histolytica*) cutaneous gangrene at abdominal or thoracic operative wound sites. These should be considered in appropriate settings[163,164] so that appropriate measures (e.g., stool examination for amebas, serologic tests, periodic acid–Schiff stain of scrapings, or biopsy of the lesion) can be undertaken to exclude this diagnosis.

Gas gangrene, anaerobic cellulitis, and other forms of crepitant cellulitis. See Chapters 94 and 246 and the section "Subcutaneous Tissue Infections and Abscesses" later in this chapter.

Gangrenous cellulitis in immunocompromised hosts. The causes of cellulitis in an immunocompromised host include agents that produce such infections in healthy individuals and other organisms not ordinarily regarded as causes of cellulitis, including gram-negative bacilli and fungi. *Pseudomonas* bacteremia may produce gangrenous cellulitis (see later section "Cutaneous Involvement in Systemic Bacterial and Mycotic Infections") in immunocompromised hosts, patients with thermal burns, and others. Mucormycotic gangrenous cellulitis may be engrafted on

FIG. 93.4 Progressive bacterial synergistic gangrene of abdominal wall. Ulcerated areas developed about wire stay sutures, which were removed. *(From Bornstein DL, Weinberg AN, Swartz MN, et al. Anaerobic infections: review of current experience.* Medicine [Baltimore]. *1964;43:207–232.)*

an extensive burn wound, or it may rarely develop in patients with diabetes mellitus, in individuals infected with human immunodeficiency virus (HIV), or in those receiving immunosuppressive therapy.[165] Local factors (e.g., open fracture sites, ileostomy stomas, fistulous tracts) also play a predisposing role in this type of infection. Spores of *Rhizopus* species (members of the Mucoraceae family) contaminating Tensoplast tape used for occlusive dressings have resulted in progressive local and disseminated infection in immunosuppressed patients.[166] The infection may exhibit an indolent course, with minimal fever and a slowly enlarging black ulcer, or it may follow a rapidly progressive febrile course. The characteristic lesion consists of a central anesthetic, black, necrotic area, with a surrounding raised zone of violaceous cellulitis and edema.[167] Superficial vesicles and blistering may occur in the gangrenous area. Skin infection usually does not result from an initial pulmonary or rhinocerebral focus, and hematogenous dissemination is not ordinarily demonstrable. Cultures of the necrotic skin or aspirates from the advancing margin usually do not reveal the fungus. Identification of the cause is best obtained from biopsy specimens—fungal wet mount of crushed tissue, tissue sections stained with hematoxylin and eosin (showing tissue and vascular invasion by characteristic broad hyphae), and culture. Necrotizing angioinvasive cellulitis caused by the zygomycete *Apophysomyces elegans* sporadically occurs in a small number of nonimmunocompromised patients after traumatic injuries potentially contaminated with soil.[168] Similarly, gangrenous skin lesions may also occur with disseminated aspergillosis in immunocompromised hosts and burn patients.

Prominent necrosis of skin and subcutaneous fat occurs rarely in patients who have chronic renal failure (with secondary hyperparathyroidism), in those receiving chronic dialysis therapy, in patients with extensive calcification of the small arteries of subcutaneous tissue, and in those in whom the calcium phosphate product is markedly elevated. Previously known as calciphylaxis, the process that results in acute local calcification is now termed *calcific uremic arteriolopathy.*[169,170] Precipitating factors for this process are poorly defined but include local trauma, hyperphosphatemia, diabetes mellitus, and systemic infection. The skin lesions begin as dark red, irregular areas resembling livedo reticularis. They become plaquelike or nodular, are painful, and rapidly increase in size but remain well demarcated. They progress to gangrenous necrosis with eschar formation. Secondary infection of necrotic areas may follow. Histologically, involved areas show extensive vascular calcification, calcinosis cutis, and ischemic skin necrosis. Bacteremia originating elsewhere may contribute to the local ischemic process through further lesional thromboses mediated by disseminated intravascular coagulopathy. These necrotic skin ulcers in patients with chronic renal failure resemble those of infective gangrenous cellulitis, particularly if they become secondarily infected.

Differential Diagnosis

The bite of the brown recluse house spider can produce a necrotizing skin lesion that resembles infectious gangrenous cellulitis. The occurrence of fever and chills 24 to 48 hours after the bite enhances the mimicry. In many cases, presumed spider bites are actually manifestations of primary MRSA cutaneous lesions, with focal skin necrosis complicating furunculosis and surrounding cellulitis.[171] The differential diagnosis of infectious gangrene and gangrenous cellulitis is presented in Table 93.5.

Presumptive Therapy

Treatment of streptococcal gangrene consists of immediate surgical exploration with longitudinal incisions extending to the deep fascia and beyond the involved gangrenous and undermined areas.[161] Distinction between streptococcal gangrenous cellulitis and streptococcal necrotizing fasciitis may be difficult before surgical exploration. Initial resuscitation measures with intravenous fluids and pressor support are essential in the presence of hypotension caused by accompanying streptococcal bacteremia or the streptococcal toxic shock syndrome. Areas of cutaneous necrosis are widely excised, and, if present, nonviable fascia is débrided. Reexploration is commonly performed within 24 hours. Antibiotic therapy consists of high-dose intravenous aqueous penicillin G (3–4 million units every 4 hours) in the setting of normal renal function. In the treatment of both streptococcal gangrene and streptococcal toxic shock, the addition of clindamycin to penicillin is recommended because it has been shown to reduce the early release of streptococcal pyrogenic exotoxin A in vitro.[21,172]

If there is any question regarding the causative agent (e.g., possibly *S. aureus* rather than group A streptococcus), vancomycin should be started empirically until MRSA can be excluded. Necrotizing fasciitis resulting from mixed anaerobes and facultative organisms (synergistic necrotizing cellulitis) can usually be suspected at the outset from the foul odor, frequent soft tissue gas, and appearance of the exudate on a Gram-stained smear. After surgery, the wound is treated with elevation and moist dressings. Skin grafting is usually required later.

Progressive bacterial synergistic gangrene can be difficult to treat. Wide excision of all necrotic tissue (extending into normal tissue), combined with broad-spectrum antibiotic treatment, is usually required. The initial use of a β-lactam–β-lactamase inhibitor combination (e.g., piperacillin-tazobactam) or a carbapenem agent (e.g., imipenem-cilastatin or meropenem), combined with vancomycin or another agent effective against MRSA, may be a reasonable empirical strategy until microbiologic data can be used to refine therapy.

Erythrasma

Erythrasma is a common superficial bacterial infection of the skin, caused by *Corynebacterium minutissimum,* a species that can be grown aerobically. It is characterized by slowly spreading, pruritic, reddish-brown macular patches, usually located in the genitocrural area, with sparing of intertriginous creases.[173] The lesions are finely scaled and finely wrinkled, and are more common in men and in obese individuals with diabetes mellitus. The disease may be asymptomatic or may undergo periodic exacerbations. Gram-stained imprints of the skin surface show large numbers of small gram-positive bacilli. Examination of the lesions under a Wood lamp reveals a distinctive coral red fluorescence.

The principal superficial skin infections to be considered in the differential diagnosis are tinea versicolor lesions on the trunk, tinea cruris (a deeper, more inflammatory, and more rapidly progressive process), and possibly candidiasis. Oral erythromycin (1.0 g/day for 5–7 days) has been efficacious in the past, with clearing of lesions within a few weeks. Topical treatment with 2% erythromycin gel[173] or an aqueous

TABLE 93.5 Differential Diagnosis of Infectious Gangrene and Gangrenous Cellulitis

	PROGRESSIVE BACTERIAL SYNERGISTIC GANGRENE	SYNERGISTIC NECROTIZING CELLULITIS[a]	STREPTOCOCCAL GANGRENE[b]	CLOSTRIDIAL MYONECROSIS (GAS GANGRENE)	NECROTIZING CUTANEOUS MUCORMYCOSIS	BACTEREMIC *PSEUDOMONAS* GANGRENOUS CELLULITIS	PYODERMA GANGRENOSUM
Predisposing Conditions	Surgery, draining sinus	Diabetes common	Occasionally diabetes or myxedema, after abdominal surgery	Local trauma	Diabetes, corticosteroid therapy	Burns, immunosuppression	Ulcerative colitis, rheumatoid arthritis
Pain	Prominent	Prominent	Prominent	Prominent	Minimal	Mild	Moderate
Systemic Toxicity	Minimal	Marked	Marked	Very marked	Variable	Marked	Minimal
Course	Slow	Rapid	Very rapid	Extremely rapid	Rapid	Rapid	Slow
Fever	Minimal or absent	Moderate	High	Moderate or high	Low grade	High	Low grade
Anesthesia of Lesion	–	–	±	–	+	±	–
Crepitus	–	Often present	–	+	–	–	–
Appearance of Involved Area	Central shaggy, necrotic ulcer surrounded by dusky margin and erythematous periphery	Crepitant cellulitis; thick, copious, foul-smelling "dishwater" drainage from scattered areas of skin necrosis	Necrosis of subcutaneous tissue and fascia with black, necrotic, "burned" appearance of overlying skin	Marked swelling, yellow-bronze discoloration of skin, brown bullae, green-black patches of necrosis, serosanguineous discharge	Usually a central black, necrotic area with a purple raised margin; may also appear as just a black ulcer	A sharply demarcated, necrotic area with black eschar and surrounding erythema resembling a decubitus ulcer; may evolve from initial hemorrhagic bulla	Begin as bullae, pustules, or erythematous nodules that ulcerate deeply; often multiple, large, and coalescing; usually on lower extremities or abdomen
Cause	Microaerophilic streptococci plus *Staphylococcus aureus* (or sometimes *Proteus)*	Usually a mixture of organisms (e.g., *Bacteroides*, peptostreptococci, *Escherichia coli*)	Primarily group A streptococci; if secondary to abdominal surgery, enteric bacteria also involved	*Clostridium perfringens* (occasionally other clostridia)	*Rhizopus, Mucor, Absidia*	*Pseudomonas aeruginosa*	Not an infection primarily; may be confused with such lesions resulting from secondary colonization by Enterobacteriaceae, microaerophilic streptococci, *P. aeruginosa,* or *S. aureus*

[a]Similar to necrotizing fasciitis type I.
[b]Necrotizing fasciitis type II.
–, Absent; +, present; ±, occasionally present.
Modified from Swartz MN. Clinical practice: cellulitis. N Engl J Med. *2004;350:904–912. Copyright ©2004 Massachusetts Medical Society.*

solution of 2% clindamycin hydrochloride can also be effective. More recently, macrolide resistance has been reported, and tetracycline or amoxicillin-clavulanate therapy has been proposed.[174] *C. minutissimum* is also the causative agent of pitted keratolysis, a superficial process consisting of crateriform pits up to 7 mm in width occurring on the pressure-bearing areas of the sole and on the ventral aspect of the toes.[175] The lesions are malodorous and are associated with hyperhidrosis.

Secondary Bacterial Infections Complicating Preexisting Skin Lesions

A variety of skin lesions (e.g., burns, eczematous dermatitides, and traumatic lesions) may become secondarily infected (see Table 93.1). Such infected lesions usually do not exhibit distinctive morphologic characteristics based on the infecting organism. Rather, the appearance of the lesions is determined to a large measure by the nature of the preexisting injury or dermatosis, such as dermatophytosis and acne conglobata, which are often treated primarily by dermatologists. Several of the other secondarily infected dermatoses have some distinctive clinical and bacteriologic features and merit brief consideration.

Diabetic Foot and Other Chronic Superficial Skin Ulcers

Decubitus Ulcers

Various aerobic, facultative, and anaerobic organisms (e.g., staphylococci, streptococci, Enterobacteriaceae, *Pseudomonas,* enterococci, peptostreptococci, *Clostridia*, and *Bacteroides* spp.) colonize and secondarily infect decubitus ulcers.[176] The extensive undermining and tissue necrosis of these ulcers and their location, frequently in proximity to the anus, provide the opportunity for invasion by anaerobes. Such lesions have been associated with bacteremias caused by *Bacteroides fragilis, Peptostreptococcus* species, *S. aureus, Enterococcus,* and various streptococci and facultative gram-negative bacilli. Cultures of the ulcer base (preferably by biopsy)[176] are sometimes helpful in guiding the selection of antibiotic therapy when there is apparent cellulitis, progressive ulceration, or systemic signs of infection. When systemic therapy is needed, broad-spectrum coverage, including anaerobic activity, is initiated and modified if necessary by subsequent culture data.

Diabetic Ulcers

Chronic foot infections in patients with diabetes mellitus are common and difficult problems.[107,177,178] They usually complicate the initially uninfected ulcerations that follow minor trauma in patients with peripheral neuropathy, chronic neuropathic ulcers, or arterial vascular insufficiency and take the form of cellulitis, soft tissue necrosis, or osteomyelitis with a draining sinus. These infections are classified depending on the extent of infection, as follows[107]:

1. Mild—if present, less than 2 cm beyond the ulcer margins
2. Moderate—more extensive or invasive infection, or both, associated with necrosis (gangrene), abscess, and deep soft tissue or skeletal involvement or both
3. Severe—the presence of systemic complications, such as fever, hypotension, and acidosis

S. aureus and β-hemolytic streptococci are frequently responsible for cellulitis or mildly infected ulcers. More chronic lesions and those previously treated with antibiotics may also contain Enterobacteriaceae or nonenteric gram-negative bacilli such as *P. aeruginosa,* or both. Malodorous wounds often indicate the presence of anaerobic pathogens. Chronic refractory ulcers, especially if associated with gangrene, are infected with a wide variety of microorganisms, including the previously mentioned pathogens as well as enterococci, diphtheroids, anaerobes, and even fungi.[179,180] Deep tissue cultures obtained through local débridement provide the most reliable bacteriologic information in diabetic foot infections. If they are not available, cultures and Gram-stained smears of material obtained from curettage of the base of the ulcer or from a purulent exudate may provide information needed to guide antimicrobial therapy. Gas present in surrounding tissues on radiologic examination may represent air introduced through the ulcer or gas generated in soft tissues by the infecting anaerobic or coliform organisms.

Antibiotic treatment of infected diabetic foot ulcers is based on meaningful bacteriologic data, if available. Initial antimicrobial treatment in a previously untreated patient with a non–limb-threatening infection is focused primarily on staphylococci and streptococci. For mild infections that can be treated at home, oral clindamycin, cephalexin, dicloxacillin, or amoxicillin-clavulanate for 2 weeks has been traditional first-line therapy. If superficial ulcers are complicated by cellulitis warranting parenteral antibiotics, intravenous cefuroxime, cefoxitin, or ampicillin-sulbactam has been recommended.[176] The incidence of MRSA has ranged between 10% and 30% in recent studies of infected diabetic foot ulcers,[180] thus requiring early culture attempts and close surveillance of patients initially treated with β-lactam agents or clindamycin. Initial antimicrobial treatment of severe or limb-threatening infections involves the use of broad-spectrum polymicrobial antibiotics against *S. aureus* (including MRSA), group B streptococci, other streptococci, Enterobacteriaceae, anaerobic gram-positive cocci, and *Bacteroides* spp. (including *B. fragilis*). Fluoroquinolone monotherapy is problematic because of possible *Bacteroides* species and other anaerobes in these infections, as well as the rising resistance observed among *S. aureus* strains and gram-negative pathogens. Currently, a variety of regimens is advocated for initial empirical therapy for limb-threatening infections[107,177]: ampicillin-sulbactam or a carbapenem, piperacillin-tazobactam, clindamycin plus a third-generation cephalosporin, and clindamycin plus a fluoroquinolone. Vancomycin is generally included as initial empirical therapy in patients with severe infection, known recent prior MRSA carriage or hospitalization or both, and residence in areas of increased MRSA prevalence. Aminoglycosides are less attractive in this setting because of the advanced age of patients and frequent associated diabetic nephropathy.

Initial surgical management includes unroofing encrusted areas, probing the wound to determine the extent of tissue destruction and possible fascial or bone involvement or both, and débriding necrotic tissue. Determining the vascular status and the extent of limb ischemia is necessary when formulating a strategic wound care program. Edema should be reduced by bed rest, elevation, and diuretic therapy, as indicated. Control of diabetes is of considerable importance. Open ulcers should be gently packed two or three times daily with sterile gauze moistened with normal saline or quarter-strength povidone-iodine (Betadine); additional wound care measures such as negative pressure dressings and topical antibiotic therapy are available, but assessments of comparative efficacy are generally lacking.[181] Surgical débridement and drainage should be carried out promptly in patients with deep ulcers extending to subcutaneous tissue or if deep tissue necrosis or suppuration is present.[107,177]

Occupation-Related Ulcers

Contaminated traumatic wounds often involve loss of skin and subcutaneous tissue, with ensuing cellulitis and deeper infections. The variety of work-associated injuries and exposures leads to a wide range of possible occupationally related infections, particularly among agricultural, aquatic, and meatpacking workers (especially those engaged in poultry and pork processing), where lacerations and degloving injuries are readily contaminated.[182–184] The bacteriology of initial wounds sustained by agricultural workers in recent series demonstrates a broad range of pathogens, including gram-negative bacilli (particularly *Enterobacter* spp. and *Stenotrophomonas maltophilia*) as well as both coagulase-positive and coagulase-negative staphylococci.[185] An often occupationally related form of cellulitis caused by *Streptococcus iniae* has occurred in those exposed to aquacultured fish, primarily tilapia (e.g., fish farmers, fish cutters, cooks).[186] *S. iniae* is a fish pathogen that has caused outbreaks of invasive disease with high mortality among tilapia in aquaculture farms or merely colonization of the surface of fish. Human infection occurs after a puncture wound of the hand by a fish bone or knife while handling or preparing fish. Cellulitis develops rapidly (within 6–24 hours after the injury). Fever, lymphangitis originating from the site of injury, and bacteremia are frequently observed. Metastatic infections such as septic arthritis, meningitis, and endocarditis may occur. Bulla formation and skin necrosis are not seen. Penicillin G is the treatment of choice, but *S. iniae* is also susceptible in vitro to cefazolin and ceftriaxone. Commercial and sport fishing or recreational activity in fresh water may result in puncture wounds or lacerations from the venomous spines of catfish.[187,188] Such wounds can be associated with local envenomation reactions and may rapidly become secondarily infected, particularly by

gram-negative bacilli found in ponds and lakes (especially *A. hydrophila,* enteric gram-negative rods such as *Edwardsiella tarda, Klebsiella,* and *E. coli*) or *Vibrio* species or *Mycobacterium marinum* in coastal waters.[189]

Posttraumatic Opportunistic Skin Infections in Immunocompromised Patients

Unusual pathogens may invade the skin of immunocompromised patients after local, often minor, lacerations or abrasions. Bacterial pathogens associated with opportunistic primary cutaneous infections include relatively commonly encountered pathogens such as *P. aeruginosa* and *Stenotrophomonas*,[190] as well as *Bacillus cereus, Nocardia,* and mycobacteria (e.g., *M. marinum, Mycobacterium haemophilum*). Primary cutaneous *B. cereus* infection can occur in neutropenic patients[191] and has been reported in a patient with severe combined immunodeficiency disease. *B. cereus* has also caused epidemic extremity infections among healthy jungle trekkers in Costa Rica after repetitive local trauma[191] and superficial scalp infection in healthy individuals after military haircuts.[192] The lesions are vesicular or pustular and usually occur on the hand or on an extremity during warm weather. Bacteremia is not a feature. Intravenously administered vancomycin is the preferred treatment.[191] Rarely, scattered papular and nodular lesions in patients with AIDS show on biopsy an abscess containing a granule consisting of basophilic-staining cocci surrounded by eosinophilic material (Splendore-Hoeppli phenomenon).[193] This particle superficially resembles a sulfur granule of actinomycosis or a mycetoma, but it is the lesion of botryomycosis and is caused by *S. aureus.*[194] Botryomycosis also occurs in immunocompetent patients; a foreign body may play a role in initiating or perpetuating the lesion, which has the gross appearance of a small infected sebaceous cyst or may resemble prurigo nodularis. Several cases of botryomycosis have occurred in patients with the hyperimmunoglobulin E syndrome associated with recurrent staphylococcal infections.

Endemic dimorphic mycoses and yeasts (e.g., blastomycosis, coccidioidomycosis, histoplasmosis, and cryptococcosis) cause skin lesions by hematogenous spread following primary pulmonary infection.[195] Most mold infections in this population are nodular or ulcerative and are acquired by traumatic inoculation (*Fusarium, Scedosporium* spp.[196]; dark-walled fungi and additional molds[197]), as are skin infections from *Prototheca*[198] (see later) and *Sporothrix schenckii. Sporothrix* and *M. marinum* infections commonly progress to nodular lymphangitis in both normal and compromised hosts; in contrast, *Nocardia* nodular lymphangitis has been recognized only in immunocompromised hosts.[199] In immunocompromised hosts, cutaneous fungal disease may reflect local inoculation but secondary spread from a pulmonary or other source can develop; disseminated infection is often present at the time cutaneous lesions are investigated.[200,201] Primary cutaneous invasive aspergillosis has been recognized with increased frequency, often in the absence of known local trauma. It appears as enlarging nodules that may undergo local necrosis and ulceration.[202] Cutaneous protothecosis (*Prototheca wickerhamii*) occurs occasionally in patients with AIDS or other immunosuppressed states,[198] and rarely in nonimmunosuppressed patients who have sustained trauma, water exposure, or local corticosteroid injections. Excision therapy or the use of amphotericin B or azole antifungal agents has been successful. A typical dermatophyte, *Trichophyton rubrum,* which ordinarily produces only superficial skin infections, may invade the deeper subcutaneous tissues of immunosuppressed hosts and produce multiple nodular or fluctuant masses; it responds to azole therapy (itraconazole or posaconazole) or terbinafine.[203]

Bacillary Angiomatosis in Patients With Acquired Immunodeficiency Syndrome

Bacillary angiomatosis (epithelioid angiomatosis) is a form of bartonellosis that involves primarily the skin but also visceral organs in patients with AIDS, occasionally in patients with other forms of immunosuppression (e.g., solid-organ transplantation), and rarely in immunocompetent individuals (e.g., at the site of healing second-degree burns; see Chapter 234).[204,205]

The lesions begin as tiny red papules that enlarge to become exophytic or pedunculated nodules, occasionally reaching 1 cm or more in diameter. Often they are dome shaped, vascular lesions, and they may possess slight surrounding erythema or a collarette of scale or both. Deeper nodules in the dermis or subcutaneous tissue are flesh colored, with a somewhat rubbery to firm consistency, and may be movable or fixed to underlying structures. The lesions bleed readily if incised. Only a few lesions may be present, or they may be quite abundant, covering the body. Oral, nasal, conjunctival, genital, and anal mucosal lesions occur. Visceral involvement takes the form of bacillary peliosis hepatis, with hypodense lesions of the liver and spleen demonstrable on abdominal computed tomography (CT). Many patients with bacillary angiomatosis have a history of cat contact or cat scratches.

The lesions of bacillary angiomatosis grossly resemble those of Kaposi sarcoma, pyogenic granuloma, hemangioma, subcutaneous tumors, or verruga peruana (eruptive phase of bartonellosis in Peru and Ecuador) and require biopsy for definitive diagnosis. Histologically, bacillary angiomatosis consists of a circumscribed, lobular proliferation of capillaries lined with prominent large endothelial cells, an inflammatory infiltrate with neutrophils, and, characteristically, aggregates of bacillary bodies that are demonstrable on Warthin-Starry silver stain. The role of *Bartonella* species as causative agents in this syndrome was demonstrated by bacterial 16S ribosomal gene analysis in infected tissue and led to the development of serologic diagnostic tests. *Bartonella henselae* and *Bartonella quintana* cause bacillary angiomatosis with equal frequency.[205]

The diagnosis of bacillary angiomatosis is made by the clinical appearance of the lesions in a patient with HIV infection and confirmed on biopsy (Warthin-Starry silver stain). Because the skin lesions are often extensive and systemic manifestations (e.g., fever, peliosis hepatis) can be features, antimicrobial treatment is indicated. Prolonged macrolide therapy is given for 3 months; doxycycline has been used in macrolide-intolerant patients, and rifampin may be added as a second agent in severely ill patients. Dramatic exacerbation of bacillary angiomatosis may rarely complicate the immune reconstitution inflammatory syndrome in treated HIV-infected patients.[206]

Hidradenitis Suppurativa

Hidradenitis suppurativa is a rather common and extremely troublesome, chronic, suppurative, cicatricial disease of apocrine glands in the axillary, genital, and perianal areas; it occurs in up to 1% of some European populations,[207] but the estimated US prevalence is only 0.05%.[208] The primary lesion appears to be unexplained keratinous plugging of the apocrine gland ducts, with early perifollicular lymphocyte infiltration and subsequent dilatation and eventual rupture of the gland with surrounding tissue inflammation,[207,209] although in some patients apocrine inflammation is dominant and, in others, keratinized epithelium is the focus of early inflammation.[209] It has been associated with certain autoimmune disorders (e.g., thyroid disease, inflammatory bowel disease, Sjögren syndrome), as well as with common conditions[210] including obesity, smoking, the metabolic syndrome,[211] and diabetes mellitus.[212] Lesional biopsies demonstrate broad suppression of the dermal innate immune response.[213] The initial lesions are tender, reddish-purple nodules that slowly become fluctuant and drain. Irregular sinus tracts are formed with repeated crops of lesions, and ultimately the involved areas show a mixture of burrowing, draining tracts and cicatricial scarring. In some patients, hidradenitis suppurativa is associated with acne conglobata or dissecting cellulitis of the scalp. In such patients, a distinctive spondyloarthropathy may occur.[214] Squamous cell carcinoma is a rare complication of hidradenitis suppurativa lesions.

Although not initially infected, the lesions frequently become infected secondarily.[215] Staphylococci, nonhemolytic streptococci, *Streptococcus anginosus* group, *E. coli, Proteus,* and *Pseudomonas* are often isolated from established draining lesions; anaerobic organisms (e.g., *Bacteroides,* anaerobic gram-positive cocci), suggested by the foul odor associated with these lesions, have also been isolated. The chronicity and localization of these lesions establishe the diagnosis of hidradenitis suppurativa, but other focal inflammatory processes should be considered in selected cases (e.g., furuncle, carbuncle, infected dermoid cyst, granuloma inguinale, lymphogranuloma venereum, infected pilonidal cyst).[215]

Treatment of hidradenitis suppurativa is difficult, particularly when the process is chronic and extensive, because of the multiple deep-seated sites of secondary infection that are inaccessible to antibiotics.[210,216] Mild disease, with isolated nonscarring nodules, responds to topical

clindamycin therapy or resorcinol. Intralesional triamcinolone is often effective to address acute flares. Moderate disease can be controlled with oral tetracycline or doxycycline monotherapy or with combination clindamycin and rifampin, although the antiinflammatory properties of these agents may account for their efficacy.[216] Disease flares associated with secondary infection may respond to oral antimicrobial therapy (based on Gram-stained smears and culture results), recognizing that resistance to maintenance topical or oral therapy is commonly present. Local moist heat to help establish drainage may also be helpful in treating the initial phases of infection. Surgical drainage is required for the management of large abscesses. In severe resistant cases exhibiting chronicity and scarring, unroofing of sinus tracts and marsupialization or radical excision of most of the involved area, followed by skin grafting, may become necessary.[210] Carbon dioxide or neodymium:yttrium-aluminum-garnet laser therapy has been effective in selected patients and avoids excisional procedures[215]; photodynamic therapy is also being investigated. Adjunctive measures including metformin, dapsone, and colchicine appear promising based on limited clinical data. Immunosuppressive therapies, including cyclosporine and tumor necrosis factor inhibitors such as infliximab and adalimumab, for the management of this chronic inflammatory condition are employed more regularly,[210,216] although clinical experience remains limited.[217]

Infected Epidermal Cysts

Epidermal cysts are closed sacs lined with proliferating epidermal cells located about the head, trunk, extremities, and vulvovaginal and scrotal areas. Lacking communication with the skin surface, they can become infected and result in abscess formation. *S. aureus* (frequently present as the sole aerobic organism) and various streptococci are the principal aerobic or facultative isolates from these abscesses. *Peptostreptococcus* and *Bacteroides* species, the primary anaerobic isolates, are often present in polymicrobial mixtures in cyst abscesses about the head, perineum, and vulvovaginal area.[218] Treatment consists principally of surgical drainage, and initial antimicrobial therapy (clindamycin, cefoxitin, or amoxicillin-clavulanate), if needed, is aimed at *S. aureus* and the probable anaerobes pending results of Gram-stained smears and cultures. Although generally localized, rupture of an infected sebaceous cyst has led to adjacent necrotizing infection.[219]

Self-Induced Skin Infections

Rarely, persisting unexplained skin ulcers are self-induced. Their colonization with a variety of gram-negative and gram-positive bacteria is inevitable. However, the continuing ulceration is the result of repeated, self-induced trauma rather than bacterial infection per se, a form of dermatitis artefacta.[220,221] Facial lesions as well as truncal and limb involvement can be seen. Very rarely, unexplained continuing or recurrent polymicrobial cellulitis or a subcutaneous abscess (particularly caused by mixed oral or intestinal flora) is the result of injection of foreign material containing saliva or other contaminated fluids into subcutaneous tissue. Examination of biopsy specimens from the involved area by polarizing microscopy may reveal the presence of birefringent foreign bodies, which suggest the true diagnosis.

Cutaneous Involvement in Systemic Bacterial and Mycotic Infections

Cutaneous manifestations may be a prominent and often diagnostic feature of various bacteremias, fungemias, and systemic bacterial infections (see Table 93.1).[222] In leptospirosis, rat-bite fever, and listeriosis, cutaneous manifestations are a small part of the total clinical picture; these conditions are considered in the chapters dealing with the responsible organisms. In some systemic infections, cutaneous manifestations are noninfectious complications of the illness (e.g., erythema nodosum, erythema multiforme, guttate psoriasis, purpura fulminans).

Bacteremias

Staphylococcus aureus

The occurrence of skin lesions (pustules, subcutaneous abscesses, purulent purpura) in the course of bacteremia or endocarditis secondary to *S. aureus* can provide an early clue to the nature of the infecting organism. The most distinctive of these lesions is purulent purpura, a small area of purpura with a white purulent center. Aspiration of the contents of the central portion reveals staphylococci and polymorphonuclear leukocytes and are typically culture positive. Rarely, scattered tender subcutaneous nodules may develop during *S. aureus* bacteremia.

Pseudomonas aeruginosa

Five types of skin lesion have been described in the course of *Pseudomonas* septicemia:

1. *Vesicles and bullae.* These lesions occur as isolated bullae or occasionally in small clusters anywhere on the skin surface. They rapidly become hemorrhagic and have a narrow encircling zone of dusky erythema. Occasionally, in infants, the lesions are surrounded by large, erythematous halos resembling insect bites or erythema multiforme.
2. *Ecthyma gangrenosum.* This lesion is a round, indurated, ulcerated, painless area with a central gray-black eschar and a surrounding narrow zone of erythema. These lesions may develop de novo, or they may evolve from an initial bullous lesion.
3. *Subcutaneous nodules.* Solitary or multiple, minimally fluctuant, subcutaneous nodules are uncommon features of *Pseudomonas* bacteremia, seen primarily in immunocompromised hosts.[223] Similar nodules in this population may have a wide range of other infectious causes—*S. aureus* and botryomycosis, mycobacterial infections, candidiasis and other deep mycoses, protothecosis, *Acanthamoeba* infection, and bacillary angiomatosis.
4. *Gangrenous cellulitis.* Gangrenous cellulitis is a superficial, sharply demarcated necrotic area that may resemble a decubitus ulcer or an area of cellulitis with edema and some necrosis of the overlying skin.
5. *Macular or maculopapular lesions.* These lesions are small, oval, erythematous macules located predominantly over the trunk that resemble the rose spots of typhoid fever. Such lesions have been reported, particularly in the tropics, in association with fever and diarrhea in the syndrome described as Shanghai fever.

These metastatic lesions typically contain numerous gram-negative bacilli but relatively few polymorphonuclear leukocytes. The development of such lesions in a febrile leukemic patient undergoing induction chemotherapy or on uninvolved skin areas of a patient with extensive thermal burns should strongly suggest the presence of *Pseudomonas* bacteremia. Presumptive antibiotic management should be aimed at *P. aeruginosa* and include a combination of an antipseudomonal β-lactam (cefepime, ceftazidime, piperacillin-tazobactam, imipenem, or meropenem) with tobramycin or a fluoroquinolone. Ecthyma gangrenosum has been associated with bacteremia caused by other gram-negative bacilli or with disseminated candidiasis at increasing frequency,[63] or it may develop as a primary necrotizing cutaneous infection in the absence of prior bacteremia (e.g., reflecting progression of *Pseudomonas* folliculitis in an immunocompromised patient).[224,225] Secondary bacteremia may develop, particularly in neutropenic patients.

Neisseria meningitidis

The skin lesions of acute meningococcemia consist of erythematous macules (initially), petechiae, purpura, and ecchymoses located on the extremities and trunk. Extensive gun-metal gray, hemorrhagic, necrotic patches can develop by confluence of petechial and purpuric lesions in fulminant meningococcemia. Symmetrical peripheral gangrene and purpura fulminans occur with prominent disseminated intravascular coagulation. Occasionally, gram-negative diplococci can be observed on smears of plasma obtained from the skin lesions of patients with acute meningococcemia.

Skin lesions are an important feature of the unusual syndrome of chronic meningococcemia, characterized by recurrent cycles of fever, arthralgia, and rash over a period of 2 to 3 months.[226,227] The rash appears in crops, each consisting of a small number of individual lesions during febrile episodes. The lesions are generally located on the extremities, particularly about joints. They may consist of erythematous maculopapules, petechiae, petechiae with vesiculopustular centers, petechiae

with small areolas of pale erythema, suggillations, or tender erythema nodosum–like nodules. Biopsy specimens of the lesions reveal the histologic picture of leukocytoclastic angiitis, a finding that may erroneously direct attention toward the diagnosis of a small vessel hypersensitivity vasculitis and away from that of vasculitis secondary to systemic infection. Biopsy of nonpurpuric erythematous areas demonstrates meningococcal adherence to the endothelium with disruption of intercellular junctions and extravasation of bacteria to the extravascular space.[228] Microbiologic confirmation of the diagnosis is challenging because of the low rate of positive cultures from blood or skin biopsy specimens; occasionally, biopsy specimens display gram-negative diplococci on Gram stain, but real-time PCR analysis of biopsy tissue can confirm the presence of *N. meningitidis*.[228]

Neisseria gonorrhoeae

The skin lesions of gonococcemia consist of a mixture of pustules surrounded by a thin zone of purpura, macules, papules, purpuric vesicles and bullae, and purpuric infarcts. The lesions are few, scattered over the distal ends of extremities in particular, and frequently painful. They are part of the gonococcemic dermatitis-arthritis syndrome.[229,230] *N. gonorrhoeae* is isolated from fewer than 5% of skin lesions, but gonococcal antigens may be identified by immunofluorescence staining or PCR of skin lesions. Cultures of the pharynx, genital sites, and joint fluid (if present) may confirm the diagnosis. In addition to arthralgias and frank arthritis, tenosynovitis may be a conspicuous feature. *N. meningitidis* can present with features closely mimicking disseminated *N. gonorrhoeae* infection.[231] Paradoxically, disseminated gonococcal infection among patients receiving the monoclonal complement inhibitor eculizumab often lacks skin lesions.[232]

Salmonella enterica Serovar Typhi

Rose spots frequently appear 7 to 10 days into the febrile course of untreated typhoid fever. The lesions are slightly raised, small (1- to 3-mm), pink papules that tend to occur in crops of 10 to 20 lesions. They are found most commonly on the upper part of the abdomen, the lower part of the chest, and the back. Rose spots are less frequently found in enteric fever caused by *Salmonella* species other than *Salmonella enterica* serovar Typhi. This organism can sometimes be found on Gram-stained preparations from the papules and isolated on culture; early antibiotic treatment (e.g., with ciprofloxacin or ceftriaxone) prevents the appearance of these skin lesions.

Haemophilus influenzae

Cellulitis involving the face, neck, or upper extremities occasionally occurs with bacteremic *H. influenzae* type b infection in children, particularly those younger than age 3 years. Although commonly described as having a peculiar purple-red or blue-red (violaceous) hue, the lesion most often is erythematous, indurated, and indistinguishable from cellulitis caused by streptococci or staphylococci. The site of primary infection is the pharynx, middle ear, or elsewhere in the upper respiratory tract. Direct invasion across traumatized buccal mucous membranes by *H. influenzae* type b colonizing the respiratory tract has been suggested as the pathogenesis of most cases of buccal cellulitis in children.[233] This infection is life threatening and acute; bacteremia (sometimes complicated by meningitis) occurs in about 80% of cases. *H. influenzae* type b cellulitis in children has almost disappeared in developed countries since widespread immunization with conjugate vaccines was introduced nearly 3 decades ago. A few cases have been reported in adults with epiglottitis or other forms of upper respiratory tract disease caused by *H. influenzae*.[234] Although adult *H. influenzae* cellulitis generally involves cervical or thoracic areas, bacteremic lower extremity *H. influenzae* type b cellulitis has been reported in normal as well as in immunocompromised adults older than age 60 years. In view of the significant rate of β-lactamase production among clinical strains of *H. influenzae* type b, initial therapy should include a third-generation cephalosporin.

Helicobacter cinaedi

An indolent syndrome of primary *H. cinaedi* bacteremia (generally without antecedent gastroenteritis) with fever and at times recurrent multifocal cellulitis has been described in immunocompromised hosts.[109,235,236] *H. cinaedi* bacteremia and cellulitis have also been observed in normal hosts, such as patients recovering from orthopedic surgery, in the course of an apparent nosocomial outbreak.[108] The cellulitis in some patients is described as having an atypical appearance—salmon pink, red-brown, or copper-colored, and lacking the expected local heat; some patients have more discrete indurated plaquelike lesions. Rarely, local pyoderma gangrenosum–like cutaneous infection without associated bacteremia may occur.[109,162] An appreciation of the rash is valuable since growth in blood cultures is often slow. *H. cinaedi* is susceptible to ceftriaxone, imipenem, tetracyclines, aminoglycosides, rifampin, and often ciprofloxacin. Prolonged therapy (2–6 weeks) is usually required to ensure resolution of symptoms and prevent recurrence.

Infective Endocarditis

The cutaneous lesions of subacute bacterial endocarditis consist of petechiae, subungual splinter hemorrhages, Osler nodes, and Janeway lesions.[237] Petechiae tend to occur in small crops, particularly in the conjunctivae, on the palate, and on the upper part of the chest and extremities, and they are the most common skin lesions of endocarditis (see Fig. 80.2). Rarely, petechiae are extremely numerous, particularly on the lower extremities, and suggest a primary vasculitis. Osler nodes are split pea–sized, erythematous, tender nodules located principally on the pads of the fingers and toes. They are few in number at any given time and occur in about 15% of patients with subacute bacterial endocarditis. The lesions are usually transient and clear in 1 to 2 days. Similar lesions may also occur in acute endocarditis (e.g., secondary to *S. aureus*). Histologic examination of such lesions in several cases of acute endocarditis has suggested septic embolization in their pathogenesis.[238] The genesis of Osler nodes in subacute bacterial endocarditis may have a different basis, perhaps sterile embolization or an allergic vasculitis. Janeway lesions (see Fig. 80.3) are painless, small, erythematous macules or minimally nodular hemorrhages in the palms or soles that occur in acute or subacute endocarditis—more commonly in the former, particularly if *S. aureus* is the cause, in which case they occur in 6% of patients.[239] Histologic findings in a case of *S. aureus* endocarditis have indicated that Janeway lesions are caused by septic microembolization.[238] Gangrenous or hemorrhagic lesions resembling Janeway lesions have been observed in marantic endocarditis[240] and in a patient with end-stage renal failure and dystrophic cardiac valvular calcification.[241]

Fungemias: *Candida albicans* and Other Yeasts

Systemic candidiasis developing in settings such as leukemia, immunosuppression, extensive antibiotic therapy, hyperalimentation, heroin addiction, or cardiac surgery may be difficult to diagnose clinically until the organism is isolated from routine blood cultures. The portal for disseminated candidiasis (or aspergillosis) may be an area of skin injured in the course of intravenous therapy (or trauma induced by adhesive tape or extravasation of intravenous fluid). Examination of the optic fundi for possible candidal endophthalmitis is sometimes helpful in making an early diagnosis of candidal fungemia while awaiting isolation of the organism from blood cultures. In neutropenic patients, the appearance of multiple, discrete (2- to 5-mm), pink maculopapules (sometimes with pale centers) on the trunk or extremities can suggest the diagnosis.[242] In some of these patients, severe diffuse muscle tenderness is present and muscle biopsy specimens have shown necrosis with yeast and pseudohyphal forms.[243] This is not entirely specific for candidiasis, because a similar presentation was seen with *Scedosporium inflatum*.[244] Disseminated cryptococcosis can also be associated with superficial (cellulitic) and deep soft tissue infection.[245] Occasionally, subcutaneous candidal abscesses may develop in the course of fungemia. Aspiration of such abscesses reveals yeasts on stained smear. Punch biopsy specimens of the maculopapular lesions provide a more accurate diagnosis than simple culture because histologic sections can reveal yeast cells in blood vessels and pseudohyphae in adjacent soft tissue. Isolation of *Candida* from an unroofed lesion may represent only surface colonization or may be consistent with *Candida* folliculitis rather than disseminated candidiasis. *M. furfur* folliculitis can be mistaken for hematogenous *Candida* lesions by appearance and histopathology.

SUBCUTANEOUS TISSUE INFECTIONS AND ABSCESSES

Exact categorization of some bacterial infections of the soft tissues (e.g., skin, subcutaneous tissue, fascia, skeletal muscle) may be difficult. Although differences between a superficial pyoderma and a necrotizing myositis such as gas gangrene are readily apparent, distinctions between many other types of soft tissue infection are sometimes blurred. Classification is usually based on features such as the anatomic structure involved, infecting organisms, and the clinical picture. Some infections may involve several components of the soft tissue, and multiple bacterial species may produce infections with the same clinical appearance.

To further compound the problem of classification, a variety of designations have been given to closely related or almost identical processes. For example, streptococcal gangrene has also been referred to as necrotizing fasciitis, but over time it became apparent that it was sometimes caused by bacteria other than group A streptococci.[21] Therefore streptococcal gangrene can be considered the major subset of necrotizing fasciitis. For convenience, because a major feature of its manifestation is cutaneous gangrene, streptococcal gangrene was considered in the preceding section with cellulitis and infectious cutaneous gangrene. Necrotizing fasciitis is reconsidered in this section on subcutaneous tissue infections, particularly in relation to its nonstreptococcal causes. Another nomenclature problem arises from infections that involve multiple soft tissue strata and that can be caused by a variety of bacterial species. For example, the condition known as synergistic necrotizing cellulitis has also been described as gram-negative anaerobic cutaneous gangrene and as synergistic nonclostridial anaerobic myonecrosis.[246,247] Because of the prominence of subcutaneous tissue involvement in this condition, it is considered primarily in this part of the chapter, although it could be considered almost as readily in the first part (see under "Cellulitis and Superficial Infections") or in the chapter on myositis (see Chapter 94). These classic and somewhat overlapping terms seem to be receding from clinical use, as the more general term *necrotizing soft tissue infection* gains popularity.[248]

Clostridial Anaerobic Cellulitis

Clostridial anaerobic cellulitis is a necrotizing clostridial infection of devitalized subcutaneous tissue. Deep fascia is not appreciably involved, and ordinarily no associated myositis is present. Gas formation is common and often extensive. Anaerobic cellulitis is several times more common than gas gangrene in war wounds.

Pathologic Characteristics and Pathogenesis

Clostridial species, usually *Clostridium perfringens,* are introduced into subcutaneous tissue through a dirty or inadequately débrided traumatic wound, through contamination at surgery, or from a preexisting localized infection. The last is frequently located in the perineum, abdominal wall, buttocks, or lower extremities, areas that are readily contaminated with fecal flora. The presence of foreign debris and necrotic tissue in the depths of a wound provides a suitable anaerobic milieu for clostridial proliferation. Very rarely, clostridial anaerobic cellulitis develops not after primary cutaneous injury but rather as a consequence of primary *C. septicum* bacteremia in the setting of leukemia and granulocytopenia.[249] Intestinal erosions are the presumed initial portals of entry. This type of *C. septicum* cellulitis must be distinguished from the even more life-threatening bacteremic *C. septicum* myonecrosis, which is often associated with a cryptic underlying colonic neoplasm (see Chapter 94).

Clinical Manifestations

The incubation period is several days, longer than the 1 to 2 days for clostridial myonecrosis. The onset is gradual, but the process may subsequently spread rapidly.[250] Local pain, tissue swelling, and systemic toxicity are not prominent features, and the relative mildness of the process helps distinguish it from true gas gangrene. The dark blebs and bronzing of the skin seen in gas gangrene are not usually features of clostridial cellulitis. Thin, dark, sometimes foul-smelling drainage from the wound (often containing fat globules) is characteristic, as is extensive tissue gas formation, which is more prominent than that observed in clostridial myonecrosis. Frank crepitus is present in the involved area and may extend widely, even beyond the limits of the active infection. *C. perfringens* cellulitis has been recurrent in the setting of retained foreign bodies.[251]

Gram-stained smears of drainage material show numerous blunt-ended, thick, gram-positive bacilli and variable numbers of polymorphonuclear leukocytes. Soft tissue radiographs show abundant gas, but not usually in the feathery linear pattern in muscles observed in clostridial myonecrosis.

Etiologic Agents

C. perfringens is the most common clostridial species responsible for this infection, but *C. septicum* and other species have been isolated. Sometimes, clostridia are present in mixed culture with facultative organisms.

Differential Diagnosis

If wound crepitus is observed, a variety of possibilities must be considered in the differential diagnosis (Table 93.6). The first is clostridial myonecrosis (gas gangrene) because of the fulminant, life-threatening nature of the infection and the requirement for emergency surgery. At the same time, distinguishing between clostridial gas gangrene and anaerobic cellulitis is essential to avoid performing unnecessarily extensive surgery. Ultimately, the two processes are differentiated in the operating room, when the wound is laid open and the viability and appearance of the muscle are observed. The muscle is normal (pink) in clostridial cellulitis but distinctly abnormal in clostridial myonecrosis: it is discolored, fails to contract on stimulation, and does not bleed from a cut surface (see Chapter 94).

Presumptive Therapy

Surgical exploration is essential to determine the presence of any muscle involvement. If no myonecrosis is found, treatment should be limited to débridement of necrotic tissue, removal of any foreign material, and drainage of pus after the wound is opened widely. Initial antimicrobial management of clostridial cellulitis requires broad-spectrum antibiotic therapy until surgical exploration has been carried out and Gram-stained smears of material from the lesion have been evaluated. Empirical therapy must cover clostridial infection (myonecrosis or anaerobic cellulitis) and necrotizing polymicrobial infection. Intravenous penicillin (2–3 million units every 3 hours or 3–4 million units every 4 hours) or ampicillin (2 g every 4 hours), plus intravenous clindamycin (0.6 g every 6–8 hours) or metronidazole (1 g loading dose followed by 0.5 g every 6 hours), provides a two-drug combination for treatment of the anaerobic organisms likely to be involved; clindamycin resistance has been reported rarely when used as monotherapy in penicillin-allergic patients and should be combined with metronidazole in these patients. Ampicillin-sulbactam (3 g every 6 hours) may also be used as initial therapy. Use of an additional antimicrobial agent (fluoroquinolone agent such as ciprofloxacin, third-generation cephalosporin, or aminoglycoside) aimed at aerobic gram-negative bacilli is based on evaluation of Gram-stained smears of exudate and tissue. Definitive selection of antimicrobial agents is subsequently based on the results of cultures and antimicrobial susceptibility tests.

Nonclostridial Anaerobic Cellulitis

A clinical picture very similar to that of clostridial anaerobic cellulitis can be produced by infection with various non–spore-forming anaerobic bacteria (e.g., *Bacteroides* species, peptostreptococci, peptococci, either alone or as mixed infections).[247] The anaerobic bacteria may be present along with facultative species (coliform bacilli, various streptococci, staphylococci) in a mixed infection. Gas-forming soft tissue infections have been produced by *E. coli, Klebsiella, Aeromonas,* and perhaps other facultative bacteria.[252]

Because the clinical features and setting are similar to those of clostridial anaerobic cellulitis, the same initial broad-spectrum antimicrobial therapy (see earlier discussion) is appropriate to cover the mixed bacterial nature of the infection. Ampicillin-sulbactam or piperacillin-tazobactam may also be used as initial therapy in conjunction with a fluoroquinolone or aminoglycoside; such double coverage broadens activity against potentially resistant gram-negative pathogens. Monotherapy with a penem agent such as meropenem may be considered.

TABLE 93.6 Differential Diagnosis of Crepitant Soft Tissue Wounds

	CLOSTRIDIAL	NONCLOSTRIDIAL ANAEROBIC CELLULITIS	CLOSTRIDIAL MYONECROSIS (GAS GANGRENE)	ANAEROBIC STREPTOCOCCAL MYOSITIS	NECROTIZING FASCIITIS (TYPE I)[b]	INFECTED VASCULAR GANGRENE	SYNERGISTIC NECROTIZING CELLULITIS[c]	NONINFECTIOUS CAUSES OF GAS IN TISSUES
Predisposing Conditions	Local trauma or surgery	Diabetes mellitus, preexisting localized infection	Local trauma or surgery	Local trauma	Diabetes mellitus, abdominal surgery, perineal infection	Peripheral arterial insufficiency	Diabetes mellitus, cardiorenal disease, obesity, perirectal infection	Mechanical effects of penetrating trauma, injuries involving the use of compressed air, entrapment of air under loosely sutured wounds or under ulcers, irrigation of wounds with hydrogen peroxide, IV catheter placement, dissection of air from tracheostomy, or spontaneous mediastinal emphysema
Incubation Period	Usually >3 d	Several days	1–2 d	3–4 d	1–4 d	>5 d	3–14 d	Less than 1 h
Onset	Gradual	Gradual or rapid	Acute	Not as rapid as gas gangrene	Acute	Gradual	Acute	Usually present immediately after trauma or manipulation; may not be recognized until examination several hours later
Pain	Mild	Mild	Marked	Marked; occurs late	Moderate or severe	Variable	Severe	Mild
Swelling	Moderate	Moderate	Marked	Moderate	Marked	Moderate or marked	Moderate or marked	Slight or absent
Skin Appearance	Minimal discoloration	Minimal discoloration	Yellow-bronze, dark bullae, green-black patches of necrosis	Erythema	Erythematous cellulitis, areas of skin necrosis	Discolored or black	Scattered areas of skin necrosis	Only those resulting from initiating trauma
Exudate	Thin, dark	Dark pus	Serosanguineous	Abundant, seropurulent	Seropurulent	None	"Dishwater" pus	None
Gas	++++	++++	++	±	++	+++	++	Variable but present; does not extend
Odor	Sometimes foul	Foul	Variable, slightly foul or peculiarly sweet	Slight, "sour"	Foul	Foul	Foul	None
Systemic Toxicity	Minimal	Moderate	Marked	Only late in course	Moderate or marked	Minimal	Marked	None
Muscle Involvement	None	None	++++	+++	None	Dead	++	None

[a]In addition to the causes of crepitant infections listed in this table, *A. hydrophila* myositis may be associated with gas in soft tissues.
[b]The term *necrotizing fasciitis* is used here to designate forms of this syndrome other than streptococcal gangrene.
[c]Synergistic necrotizing cellulitis is essentially the same process as type I necrotizing fasciitis. Because the former occasionally tends to involve muscle, it is given a separate designation here; however, the two processes are clinically indistinguishable in most cases.
IV, Intravenous; ±, rarely present; ++, present to mild extent; +++, present to moderate extent; ++++, extensive.
Modified from Finegold SM. Anaerobic Bacteria in Human Disease. *New York: Academic Press; 1977.*

Evaluation of Gram-stained smears of exudate aspirated from the lesion supplies a more focused basis for initial antimicrobial therapy. Subsequent results of cultures and susceptibility testing of aspirates or tissue removed at surgical exploration provide the information needed for narrowing (or extending) antimicrobial therapy. The surgical approach used is the same as for the treatment of clostridial anaerobic cellulitis.

Necrotizing Fasciitis

The term *necrotizing fasciitis* encompasses at least three distinct bacteriologic entities.[21,253,254] In type I (polymicrobial) necrotizing fasciitis, at least one anaerobic species (most commonly *Bacteroides* or *Peptostreptococcus*) is isolated in combination with one or more facultative anaerobic species, such as streptococci (other than group A) and members of the Enterobacteriaceae (e.g., *E. coli, Enterobacter, Klebsiella, Proteus*). An obligate aerobe such as *P. aeruginosa* is only rarely a component of such a mixed infection. Cases in which only anaerobes are present appear to be rare. In type II disease, generally attributed to monomicrobial infection and most commonly due to group A streptococci (also known as hemolytic streptococcal gangrene), group A streptococci are isolated alone or in combination with other species, most commonly *S. aureus.* Recognition of type III necrotizing fasciitis due to infection solely by marine gram-negative pathogens such as *Vibrio* species or *Aeromonas hydrophila* has been proposed.[253,254]

Classification of necrotizing fasciitis syndromes continues to evolve. Monomicrobial gram negative infections due to Klebsiella[255] and other Enterobacteriaceae[256] have been reported predominantly in Asian populations, particularly among diabetics.[256] Monomicrobial necrotizing fasciitis due to miscellaneous gram-negative infections such as *P. multocida* and *H. influenzae,* have also been reported.[257] In addition, fungal necrotizing fasciitis due to both yeasts and true molds have been documented and proposed as representing a fourth type of necrotizing fasciitis.[257] Streptococcal gangrene was considered in the first part of this chapter as a form of gangrenous cellulitis. In this section, specific comments about streptococcal gangrene are limited to the expanded setting in which the disease can appear and the changes in clinical features noted with the recent apparent increase in bacteremic and severe invasive group A streptococcal infections and their association with the streptococcal toxic shock–like syndrome.[4,159,160]

Hemolytic streptococcal gangrene occurs after minor trauma, stab wounds, or surgery, particularly in the context of diabetes and peripheral vascular disease, but cirrhosis and corticosteroid therapy have also been predisposing factors.[159] In outbreaks of streptococcal toxic shock–like syndrome, chills, fever (or profound hypothermia and shock), confusion, vomiting, diarrhea, tachycardia, hypotension, and multiorgan failure are prominent features. Necrotizing fasciitis is present in about half of cases of streptococcal toxic shock–like syndrome.[4,160] Streptococcal strains of M protein types 1, 3, 12, and 28 are most commonly involved and, in the United States, they usually elaborate pyrogenic exotoxin A. The role of nonsteroidal antiinflammatory drugs as a risk factor for developing necrotizing fasciitis or increasing the rate of complications in this setting continues to be debated.[258,259] These agents may simply delay timely diagnosis by reducing pain and local inflammatory findings, or may act as an important accelerator of necrotizing infection by reducing prostaglandin production and increasing the production of proinflammatory cytokines.[259] Leukocytosis, thrombocytopenia, azotemia, and increased serum levels of creatine phosphokinase are commonly present. Increasing creatine phosphokinase levels may serve as an indication of progression of streptococcal cellulitis to necrotizing fasciitis and myositis. Unlike many earlier cases of hemolytic streptococcal gangrene, which affected older individuals with underlying diseases, more recently streptococcal toxic shock syndrome has occurred primarily in young, previously healthy adults after minor trauma.[260] In 70% of patients, soft tissue findings progressed to hemolytic streptococcal gangrene with the development of vesicles, violaceous bullae, and necrosis of subcutaneous tissues typical of necrotizing fasciitis (or myositis) requiring surgical débridement.[260] The mortality rate was about 30%. In young children, the skin lesions of varicella can be superinfected with group A streptococci and become a major risk factor for group A streptococcal necrotizing fasciitis.[261]

In patients with severe, invasive group A streptococcal infection, a primary site of infection generally involving skin and soft tissue is identifiable in roughly 75% of cases, with necrotizing fasciitis present in most of these patients.[160] There is a high rate of streptococcal bacteremia. The pathogenesis of streptococcal toxic shock appears to involve microbial and host factors. The predominant group A streptococci isolated in several outbreaks have expressed the common M protein type M1 or M3 (although other M types are also associated with this syndrome) and are classified in the tissue-tropic *emm* families D and E; they possess pyrogenic exotoxin gene *speA* or *speC* and express pyrogenic exotoxins in vitro.[262] Genome microarray analysis has demonstrated that M1 and M3 strains carry several additional unique virulence factors that may be responsible for the apparent association of these strains with invasive infection.[263] Host susceptibility to streptococcal toxic shock syndrome may be related to an absence of suitable protective antibodies against the M protein of invading streptococci as well as against the pyrogenic exotoxins. Such seronegative individuals would be expected to be at heightened risk for invasive streptococcal infection and toxic shock syndrome,[160] but a recent multicenter retrospective cohort study of pressor-dependent patients with necrotizing fasciitis, involving over 4000 patients at 121 centers, found that intravenous immune globulin therapy was actually administered in only 4% of patients and had no effect on survival or hospital length of stay.[264] Because the streptococcal pyrogenic exotoxins act as superantigens, which activate T cells by binding to human leukocyte antigen (HLA) class II molecules, protection against or heightened susceptibility to streptococcal toxic shock may correlate with certain HLA-DQ polymorphisms.[265] The more general features of necrotizing fasciitis are now considered.

Clinical Manifestations

Necrotizing fasciitis is an uncommon severe infection involving the subcutaneous soft tissues, particularly the superficial (and often the deep) fascia. It is usually an acute process but rarely may follow a subacute progressive course. Necrotizing fasciitis can affect any part of the body but is most common on the extremities, particularly the legs. Extremity involvement is particularly common with type II (group A streptococcal) necrotizing fasciitis; abdominal wall, perianal and groin areas, and postoperative wounds are more common with type I (polymicrobial) infections.[253,254] The portal of entry is usually a site of trauma, often minor (e.g., laceration, abrasion, burn, insect bite); a laparotomy performed in the presence of peritoneal soiling[266] (e.g., penetrating abdominal trauma or perforated viscus) or another surgical procedure (e.g., hemorrhoidectomy, vasectomy); perirectal abscess; decubitus ulcer; or intestinal perforation. The last may be secondary to occult diverticulitis,[267] rectosigmoid neoplasm, perforated appendicitis, or a foreign body such as a chicken bone or toothpick. Necrotizing fasciitis from such intestinal sources may present in the lower extremity (extension along the psoas muscle),[267] as well as in the groin or abdominal wall (via a colocutaneous fistula). Particular clinical settings in which necrotizing fasciitis may develop include diabetes mellitus,[253] alcoholism, and parenteral drug abuse,[268] often following "skin popping."[268,269]

In the neonate, necrotizing fasciitis can be a serious complication of omphalitis. Initial swelling and erythema about the umbilicus can progress over several hours to several days and result in purplish discoloration and periumbilical necrosis.[270] Involvement of the anterior abdominal wall frequently extends to the flanks and even onto the chest wall.

The affected area is initially erythematous, swollen, without sharp margins, hot, shiny, exquisitely tender, and painful.[253,254,271] Lymphangitis and lymphadenitis are infrequent. The process progresses rapidly over hours to days, with sequential skin color changes from red-purple to patches of blue-gray. Within 3 to 5 days after onset, skin breakdown with bullae (containing thick pink or purple fluid) and frank cutaneous gangrene (resembling a thermal burn) can be seen. By this time, the involved area is no longer tender but rather has become anesthetic secondary to thrombosis of small blood vessels and destruction of superficial nerves located in the necrotic, undermined subcutaneous tissue. The onset of anesthesia may antedate the appearance of skin necrosis and provide a clue that the process is necrotizing fasciitis and not a simple cellulitis. Marked swelling and edema may produce a

compartment syndrome especially with extremity involvement, with complicating extensive myonecrosis requiring prompt fasciotomy. Measurement of compartment pressure may aid the evaluation in early situations in which marked pain and swelling are present without concomitant skin changes that would indicate the diagnosis.[4] Subcutaneous gas is often present in the polymicrobial form of necrotizing fasciitis, particularly in patients with diabetes mellitus. Systemic toxicity is prominent, and the temperature is often, but not universally, elevated in the range of 38.9°C to 40.5°C (102°F–105°F). Immunosuppressed individuals may lack fever or systemic toxicity, making the diagnosis particularly challenging. On probing the lesion with a hemostat through a limited incision, the instrument easily passes along a plane just superficial to the deep fascia. Such easy passage would not occur with ordinary cellulitis.

Leukocytosis is commonly present; hyponatremia and azotemia underscore the likelihood of necrotizing infection.[272] Gram-stained smears of exudate usually reveal a mixture of organisms or, in the case of streptococcal gangrene, chains of gram-positive cocci. Rarely, a single population of gram-negative rods can be seen, suggesting type III necrotizing fasciitis. In one case, we observed numerous long, gram-positive bacilli with subterminal spores (along with gram-negative bacilli) in the foul-smelling, purulent exudate of a patient with crepitant necrotizing fasciitis after a lower leg amputation for peripheral vascular disease. The presence of numerous spores in the wound exudate indicated that the gram-positive bacilli were unlikely to be *C. perfringens.* Before surgery, the patient had *Clostridioides difficile* (formerly *Clostridium difficile*) enterocolitis, and *C. difficile* was isolated along with several members of Enterobacteriaceae from the wound drainage material.

Blood cultures are frequently positive. Hypocalcemia (without tetany) may occur if necrosis of subcutaneous fat is extensive.

Fournier gangrene. A form of necrotizing fasciitis occurring about the male genitalia and the perineum of both sexes is known as Fournier gangrene[21,273,274] and also as idiopathic gangrene of the scrotum, streptococcal scrotal gangrene, and perineal phlegmon. It may be confined to the penis or scrotum, or it may extend to involve the perineum, penis, and abdominal wall. Although typically seen in individuals over the age of 50, it may occur in children and young adults.[275] Systemic predisposing factors include diabetes mellitus, obesity, smoking, vascular disease, immunocompromised states (including HIV infection), local trauma, paraphimosis, periurethral extravasation of urine, perirectal or perianal infection,[276] and surgery in the area (circumcision, herniorrhaphy, Bartholin abscess). In cases originating in the genitalia, the infecting bacteria probably penetrate the urethra and paraurethral glands. Once infection penetrates Buck fascia of the penis, it can spread along the contiguous fascias of the scrotum and penis (dartos fascia), Colles fascia of the perineum, and Scarpa fascia of the anterior abdominal wall.[277,278] Anaerobic bacteria play an important role and contribute to the typical foul odor associated with this form of necrotizing fasciitis. Mixed cultures containing facultative organisms (*E. coli, Klebsiella,* other Enterobacteriaceae, enterococci), along with anaerobes *(Bacteroides, Fusobacterium, Clostridium,* anaerobic or microaerophilic streptococci), and occasionally *C. albicans,*[277] have been obtained from studied cases.[273,279] *S. aureus* and various β-hemolytic streptococci occur in roughly one-third of patients[279]; rarely, group A streptococcal gangrene evolving from streptococcal balanitis can also involve the male genital area. Multidrug-resistant organisms are increasingly common, including *Acetinobacter* in some series, underscoring the importance of initial broad-spectrum antibiotic therapy.[280]

The infection commonly starts as cellulitis adjacent to the portal of entry. Early in the course of Fournier gangrene, the involved area is swollen, erythematous, and tender as the infection begins to involve the deep fascia. Pain is prominent; fever and systemic toxicity are marked. Swelling and crepitus of the scrotum quickly increase, and dark purple areas develop and progress to extensive scrotal gangrene. If the abdominal wall becomes involved in an obese patient with diabetes, the process can spread extremely rapidly.

Other special anatomic forms of necrotizing fasciitis. Necrotizing fasciitis of the face and eyelids,[281] neck,[282,283] and lips is uncommon but life threatening. It is most often caused by group A streptococci, alone or with *S. aureus,* and represents streptococcal gangrene; occasionally, it represents mixed infections of group A streptococcus with Enterobacteriaceae or oral *Bacteroides* species. Although necrotizing fasciitis of the head and neck is often considered a single entity, in fact it represents two conditions etiologically.[284] Craniofacial necrotizing fasciitis is commonly caused by group A streptococci or *S. aureus,* whereas cervical necrotizing fasciitis often represents a polymicrobial process (e.g., group A streptococci, various other streptococcal species, *Bacteroides* or *Peptostreptococcus* spp.). In mixed infections, crepitus may be a feature, as may necrosis of the epidermis and superficial fascia. Trauma is the usual precipitating cause of necrotizing fasciitis of the periorbital areas and face; dental, oral (including sialoadenitis), and pharyngeal infections predispose to cervical necrotizing fasciitis. Differentiation of the latter from cervical soft tissue infection of odontogenic origin can be difficult, but rapid spread of infection to other areas of the neck, severe pain, and systemic symptoms along with subcutaneous crepitus suggest the diagnosis of necrotizing fasciitis. If crepitus is not palpable, soft tissue radiography or prompt CT may help in the diagnosis by demonstrating subcutaneous gas. The mortality associated with cervical necrotizing fasciitis is about four times as high as that from craniofacial necrotizing fasciitis.[284]

Other microbial causes of necrotizing fasciitis. Various pathogens have been occasionally recovered from wounds and often from blood cultures of patients with necrotizing fasciitis. Gram-negative necrotizing fasciitis due to *A. hydrophila* has been reported after open trauma. Immunocompromised hosts, including neutropenic children receiving cancer chemotherapy, are at risk for necrotizing fasciitis caused by *P. aeruginosa* or Enterobacteriaceae.[285] The acute cellulitis caused by *V. vulnificus* and other *Vibrio* species (described earlier) may extend to the superficial and deep fascia and produce necrotizing fasciitis. Similarly, MRSA may cause necrotizing fasciitis, usually in HIV-infected or other immunocompromised hosts.[286] Very rare causes of necrotizing fasciitis include nasopharyngeal pathogens such as *S. pneumoniae* and *H. influenzae* type b, food-associated pathogens (*Listeria monocytogenes, Salmonella* spp.), and environmental species such as *A. hydrophila, Elizabethkingia meningoseptica, Chryseobacterium* species, *Ochrobactrum anthropi*, and *Serratia marcescens.* The uncommonly encountered necrotizing fasciitis caused by *S. marcescens* has been the subject of case reviews that have emphasized its high mortality.[287,288]

Differential Diagnosis

Table 93.6 details the differential diagnosis of necrotizing fasciitis. Necrotizing neutrophilic dermatoses, including progressive pyoderma gangrenosum and necrotizing Sweet syndrome, can present with systemic features including shock, and can mimic necrotizing fasciitis.[289]

Prompt diagnosis is of paramount importance because of the rapidity with which the process can progress. The reported mortality rate of necrotizing fasciitis has approached 35% overall and is somewhat less (15%) for Fournier gangrene[273,274]; current analyses demonstrate improved survival overall (~15%).[290,291] Prompt diagnosis is generally associated with enhanced survival. Early clinical differentiation of necrotizing fasciitis from cellulitis can be difficult because the initial signs—including pain, edema, and erythema—are not distinctive, particularly when deep trunk or retroperitoneal sites are involved.. However, the presence of severe pain or marked systemic toxicity out of proportion to the local findings should alert the physician to this possibility. Although CT and magnetic resonance imaging (MRI) can demonstrate subcutaneous and fascial edema, as well as tissue gas, in patients with necrotizing fasciitis and can distinguish this process from cellulitis, delay of definitive surgical treatment, such as can occur with the use of MRI, should be avoided.[292,293] Ultrasonography and CT are more rapidly performed and have occasionally been helpful for assessing possible Fournier gangrene when local scrotal inflammatory findings are present but cutaneous necrotizing infection or crepitus is not apparent.[294,295] However, in patients in whom the diagnosis is clearly suspected, the most expeditious route to diagnosis is through surgical exploration or biopsy, without introducing delay for imaging studies. Characteristic abnormalities are readily seen upon exposing the deep subcutaneous tissues, with discolored and edematous tissue, local necrosis, and a characteristic thin exudate. Blunt dissection readily separates the tissues planes due to local spread and undermining of the adjacent tissue.[248]

Imaging studies can be most useful early in the process, when pain and swelling are evident but cutaneous changes are absent and the diagnosis is uncertain. Imaging studies may also be helpful for monitoring clinical progress after surgical débridement, when further surgery may need to be considered. Additionally, imaging studies are useful in the diagnosis and management of necrotizing fasciitis in areas of the body in which the process is more inaccessible (e.g., retroperitoneal involvement[296]) or may readily spread to other tissue compartments (e.g., cervical fasciitis spreading to the mediastinum, pleura, and pericardium). Several imaging findings (e.g., fascial thickening) are actually nonspecific, and distinguishing between a surgical emergency and an inflammatory fasciitis syndrome is based on the dramatic clinical features.[297] Frozen-section examination of biopsy specimens (including dermis, infected subcutaneous tissue, fascia, and underlying muscle) has been found to be helpful for early diagnosis.[298]

Presumptive Therapy

Once the diagnosis is made, immediate surgical débridement is essential. In patients in whom the diagnosis is clearly suspected on clinical grounds (deep pain with patchy areas of surface hypoesthesia, crepitation, or bullae and skin necrosis), direct operative intervention is indicated. Extensive incisions should be made through the skin and subcutaneous tissues and should go beyond the area of apparent involvement until normal fascia is found. Necrotic fat and fascia should be excised, and the wound should be left open. A second-look procedure is frequently necessary 24 hours later to ensure adequacy of the initial débridement.[253,254] In the case of Fournier gangrene, orchiectomy is not usually necessary because the testes have their own blood supply originating from the retroperitoneum, independent of the compromised fascial and cutaneous circulation of the scrotum. Initial antimicrobial therapy is based on the evidence for prominent roles of anaerobic bacteria, Enterobacteriaceae, and various streptococci in this process and on the specific findings on Gram-stained smears. The relatively frequent presence of *S. aureus* (approximately 20%) further complicates initial antibiotic management. Antibiotics used before bacteriologic data are obtained include combinations of vancomycin, cefepime, gentamicin, and metronidazole; vancomycin, piperacillin-tazobactam, and gentamicin; and vancomycin with imipenem or meropenem. Patients intolerant of vancomycin should receive linezolid or daptomycin until assessment of resistant gram-positive pathogens is completed. Aminoglycosides must be used cautiously and monitored closely, since there is a high rate of acute kidney injury in these patients. A fluoroquinolone such as ciprofloxacin is often administered rather than gentamicin owing to impaired renal function at presentation. For group A streptococcal necrotizing fasciitis, penicillin or ampicillin plus clindamycin is recommended.

Several ancillary therapies, none of which are substitutes for prompt surgical débridement or of proven efficacy, have been described. One is the use of intravenous immune globulin to treat the streptococcal toxic shock syndrome accompanying the treatment of group A streptococcal necrotizing fasciitis.[4,262,299] A recent large-scale retrospective cohort analysis demonstrated that intravenous immune globulin administration did not have a demonstrable effect on survival or length of hospital stay.[264] The other is the use of hyperbaric oxygen for the treatment of polymicrobial necrotizing fasciitis, particularly of the trunk.[272,300] A large Australian retrospective study demonstrated a statistically significant reduction in mortality among recipients of hyperbaric oxygen therapy, but many potential biases confound such analysis.[301] This modality is not widely available and should not delay urgent débridement and conventional therapy with appropriate antibiotics and intensive care supportive measures (also see Chapter 50).

Synergistic Necrotizing Cellulitis

Clinical Manifestations

Synergistic necrotizing cellulitis (gram-negative anaerobic cutaneous gangrene, necrotizing cutaneous myositis, synergistic nonclostridial anaerobic myonecrosis) is a variant of necrotizing fasciitis, with prominent involvement of skin and muscle and of subcutaneous tissue and fascia. Some cases of Fournier gangrene extending onto the abdominal wall are examples of this condition. Predisposing factors include diabetes mellitus, obesity, advanced age, and cardiorenal disease. Most infections are located on the lower extremities or near the perineum (e.g., originating in a perirectal abscess).[246] The lesion may first be manifested as small skin ulcers draining foul-smelling, reddish-brown (dishwater) pus. Circumscribed areas of blue-gray gangrene surround these draining sites, but the intervening skin appears normal despite necrosis of underlying subcutaneous tissue, fascia, and muscle. Local pain and tenderness are marked. Tissue gas is apparent in about 25% of patients. Systemic toxicity is a feature; about 50% of patients have bacteremia.

Etiologic Agents

Cultures consistently show mixtures of anaerobic bacteria (anaerobic streptococci, *Bacteroides,* or both) and facultative bacteria *(Klebsiella, Enterobacter, E. coli, Proteus),*[246] similar to other necrotizing soft tissue processes, although monomicrobial infection (e.g., due to *B. cereus*) has been reported.

Presumptive Therapy

Initial surgery involves incision and drainage, as with necrotizing fasciitis, but radical débridement is often necessary because of extensive involvement of deep fascia and muscle.[246] Amputation may be required. Antibiotic management is initially based on the results of Gram-stained smears of wound exudates, but it should include an antimicrobial agent effective against *Bacteroides* (see earlier discussion of presumptive therapy for type I necrotizing fasciitis).

Miscellaneous Infections Secondary to Trauma

Bite Infections

Infections secondary to bites are discussed in Chapter 315.[302–304]

Burn Infections

Infections secondary to burns are discussed in Chapter 314.

Injection Site Abscesses

Subcutaneous and intramuscular abscesses infrequently occur after therapeutic injections. *S. aureus,* facultative gram-negative bacilli, and anaerobic bacteria are usually implicated. Hematomas may represent sites of delayed infection. Gas gangrene has occurred after various injections, including insulin[305] and aqueous epinephrine. Opportunistic infections, including mucormycosis, have complicated insulin injections in immunocompromised hosts.[306] Subcutaneous and intramuscular abscesses caused by a variety of oral anaerobes and streptococci have occurred after skin popping or attempted intravenous injections by narcotic addicts.[247,307] Injection-related anthrax is being increasingly recognized in the United Kingdom.[64] In the case of subcutaneous abscesses secondary to intravenous drug abuse, vascular ultrasonography may be helpful regarding the need for excision of involved veins, which often contain pus (suppurative thrombophlebitis) or an infected thrombus,[307,308] in addition to débridement and drainage.

Factitial Disease (Self-Induced Abscesses)

Occasionally, subcutaneous abscesses and cellulitis are produced when a patient deliberately injects or inserts contaminated substances into the skin.[309,310] Such abscesses are often recurrent and may be of monomicrobial or polymicrobial origin, usually consisting of oral or fecal flora. Sterile abscesses may be induced by the introduction of foreign material without bacterial contamination. Such foreign material may be identified by examination of biopsy specimens with polarizing microscopy.

Subcutaneous Infections Originating in Contiguous Foci

Osteomyelitis

Occasionally, most commonly in a child, acute hematogenous osteomyelitis is manifested as a subcutaneous abscess (see also Chapter 104). Under these circumstances, a subperiosteal abscess has ruptured through intervening tissue into the subcutaneous tissue. *S. aureus* is the most common causative agent in such infections. It is important to recognize the nature of the process because of the different therapeutic

programs required for osteomyelitis and for a subcutaneous abscess of cutaneous origin. Involvement of subcutaneous tissue as a consequence of osteomyelitis may also occur in the form of a draining sinus associated with chronic osteomyelitis and sequestrum formation. Multiple draining sinuses may occur as a result of multiple foci of osteomyelitis in disseminated blastomycosis. Routine radiographs may demonstrate underlying osteomyelitis in relation to the observed subcutaneous abscess; in acute osteomyelitis, MRI will be diagnostic, even when conventional studies are nondiagnostic.

Actinomycosis

Subcutaneous abscesses frequently develop in the course of cervical, thoracic, or sometimes abdominal actinomycosis. Draining sinuses ultimately result (see Chapter 254).

Primary Pyodermas

On occasion, more superficial skin infections beginning as folliculitis, furunculosis, or cellulitis may progress into the deeper subcutaneous tissue and form a subcutaneous (sometimes cold) abscess. *S. aureus* is commonly the cause. Such progression occurring repeatedly might suggest certain underlying phagocytic cell defects, such as chronic granulomatous disease of childhood[311] or hyperimmunoglobulin E syndrome (Job syndrome).[312,312a] These disorders are discussed further in relation to suspected immunodeficiency states in Chapter 12.

In a cataloguing of the bacteriology of a large number of cutaneous abscesses (with unspecified individual predisposing causes), *S. aureus* was the single most common aerobic-facultative isolate, followed in frequency by groupable (A, B, C, D) and nongroupable streptococci.[218] Among anaerobic isolates, *Bacteroides* species (most commonly the *B. fragilis* group) were most frequent, followed by *Peptostreptococcus* and *Clostridium* species. These abscesses are commonly polymicrobial (mixed aerobic-anaerobic). As might be predicted, *S. aureus* is the principal isolate in infections (both abscesses and wounds) of the extremities and trunk, whereas anaerobes are more numerous than aerobic facultative species in such infections in the genital, perirectal, inguinal, and head and neck areas.

Subcutaneous Abscesses in the Course of Bacteremic Infections

Metastatic pyogenic infections can occur during the course of bacteremias or endocarditis caused by various common invasive organisms (e.g., *S. aureus*) in subcutaneous tissue, as well as other organs and tissues. These abscesses are tender and fluctuant. Rarely, multiple, firm, nodular subcutaneous lesions clinically resembling those of Weber-Christian disease occur in the course of a staphylococcal bacteremia. If promptly identified and treated, the process may be aborted before frank abscess formation occurs. Other pathogens that commonly cause bacteremia but are only rarely associated with metastatic subcutaneous abscesses include *Streptococcus pneumoniae*[313] and *V. vulnificus*.[314] Conversely, bacterial pathogens that are infrequently responsible for bacteremia (e.g., *Nocardia* spp.,[315] *Corynebacterium jeikeium*[316]) may also occasionally produce metastatic cutaneous abscesses in immunocompromised or debilitated individuals.

Mycetoma

See Chapter 261.

Key References

The complete reference list is available online at Expert Consult.

4. Bisno AL, Stevens DL. Streptococcal infections of skin and soft tissues. *N Engl J Med*. 1996;334:240–245.
13. Zetola N, Francis JS, Nuermberger EL, et al. Community-acquired methicillin-resistant *Staphylococcus aureus:* an emerging threat. *Lancet Infect Dis*. 2005;5:275–286.
21. Stevens DL, Bisno AL, Chambers HF, et al; Infectious Diseases Society of America. Practice guidelines for the diagnosis and management of skin and soft-tissue infections. *Clin Infect Dis*. 2005;41:1373–1406.
26. Stanley JR, Amagai M. Pemphigus, bullous impetigo, and the staphylococcal scalded-skin syndrome. *N Engl J Med*. 2006;355:1800–1810.
33. Lappin E, Ferguson AJ. Gram-positive toxic shock syndromes. *Lancet Infect Dis*. 2009;9:281–290.
49. Sladden MJ, Johnston GA. More common skin infections in children. *BMJ*. 2005;330:1194–1198.
54. Johnston SL. Clinical immunology review series: an approach to the patient with recurrent superficial abscesses. *Clin Exp Immunol*. 2008;152:397–405.
55. Demos M, McLeod MP, Nouri K. Recurrent furunculosis: a review of the literature. *Br J Dermatol*. 2012;167:725–732.
57. Ammerlaan HS, Kluytmans JA, Wertheim HF, et al. Eradication of methicillin-resistant *Staphylococcus aureus* carriage: a systematic review. *Clin Infect Dis*. 2009;48:922–930.
58. Simor AE, Phillips E, McGeer A, et al. Randomized controlled trial of chlorhexidine gluconate for washing, intranasal mupirocin, and rifampin and doxycycline versus no treatment for the eradication of methicillin-resistant *Staphylococcus aureus* colonization. *Clin Infect Dis*. 2007;44:178–185.
59. Fritz SA, Hogan PG, Camins BC, et al. Mupirocin and chlorhexidine resistance in *Staphylococcus aureus* in patients with community-onset skin and soft tissue infections. *Antimicrob Agents Chemother*. 2013;57:559–568.
61. Wasserzug O, Valinsky L, Klement E, et al. A cluster of ecthyma outbreaks caused by a single clone of invasive and highly infective *Streptococcus pyogenes*. *Clin Infect Dis*. 2009;48:1213–1219.
68. Swartz MN. Recognition and treatment of anthrax: an update. *N Engl J Med*. 2001;345:1621–1626.
84. Leclerc S, Teixeira A, Mahé E, et al. Recurrent erysipelas: 47 cases. *Dermatology*. 2007;214:52–57.
102. Swartz MN. Cellulitis. *N Engl J Med*. 2004;350:904–912.
107. Lipsky BA, Berendt AR, Cornia PB, et al. 2012 Infectious Diseases Society of America clinical practice guideline for the diagnosis and treatment of diabetic foot infections. *Clin Infect Dis*. 2012;54:e132–e173.
111. Brooke CJ, Riley TV. *Erysipelothrix rhusiopathiae:* bacteriology, epidemiology and clinical manifestations of an occupational pathogen. *J Med Microbiol*. 1999;48:789–799.
112. Lewin MR, Knott P, Lo M. Seal finger. *Lancet*. 2004;364:448.
114. Gold WL, Salit IE. *Aeromonas hydrophila* infections of skin and soft tissue: report of 11 cases and review. *Clin Infect Dis*. 1993;16:69–74.
116. Dechet AM, Yu PA, Koram N, et al. Nonfoodborne *Vibrio* infections: an important cause of morbidity and mortality in the United States, 1997-2006. *Clin Infect Dis*. 2008;46:970–976.
131. Majeed HA, Quabazard Z, Hijasi Z, et al. The cutaneous manifestations in children with familial Mediterranean fever (recurrent hereditary polyserositis): a six-year study. *QJM*. 1990;75:607–616.
132. Abbas O, Kibbi AG, Rubeiz N. Sweet's syndrome: retrospective study of clinical and histologic features of 44 cases from a tertiary care center. *Int J Dermatol*. 2010;49:1244–1249.
136. Green WH, Yosipovitch G, Pichardo RO. Recurrent, pruritic dermal plaques and bullae. Diagnosis: eosinophilic cellulitis (Wells syndrome). *Arch Dermatol*. 2007;143:791–796.
138. Faber K, Schroeder L, Thill M-P, et al. Carcinoma erysipeloides of the neck. *Lancet*. 2002;359:1025.
139. Gunderson CG. Cellulitis: definition, etiology, and clinical features. *Am J Med*. 2011;124:1113–1122.
140. Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children. *Clin Infect Dis*. 2011;52:e18–e55.
146. Miller LG, Daum RS, Creech CB, et al. Clindamycin versus trimethoprim-sulfamethoxazole for uncomplicated skin infections. *N Engl J Med*. 2015;372:1093–1103.
147. Wessels MR. Choosing an antibiotic for skin infections. *N Engl J Med*. 2015;372:1164–1165.
148. Talan DA, Mower WR, Krishnadasan A, et al. Trimethoprim-sulfamethoxazole versus placebo for uncomplicated skin abscess. *N Engl J Med*. 2016;374:823–832.
150. Thomas KS, Crook AM, Nunn AJ, et al; U.K. Dermatology Clinical Trials Network's PATCH I Trial Team. Penicillin to prevent recurrent leg cellulitis. *N Engl J Med*. 2013;368:1695–1703.
153. Lowe CF, Bernard KA, Romney MG. Cutaneous diphtheria in the urban poor population of Vancouver, British Columbia, Canada: a 10-year review. *J Clin Microbiol*. 2011;49:2664–2666.
155. Belsey MA, Sinclair M, Roder MR, et al. *Corynebacterium diphtheriae* skin infections in Alabama and Louisiana: a factor in the epidemiology of diphtheria. *N Engl J Med*. 1969;280:135–141.
160. Stevens DL. Streptococcal toxic-shock syndrome: spectrum of disease, pathogenesis, and new concepts in treatment. *Emerg Infect Dis*. 1995;1:69–78.
163. Davson J, Jones DM, Turner L. Diagnosis of Meleney's synergistic gangrene. *Br J Surg*. 1988;75:267–271.
173. Miller SD, David-Bajar K. Images in clinical medicine. a brilliant case of erythrasma. *N Engl J Med*. 2004;351:1666.
176. Bowler PG, Duerden BI, Armstrong DG. Wound microbiology and associated approaches to wound management. *Clin Microbiol Rev*. 2001;8:244–269.
183. Haagsma JA, Tariq L, Heederik DJ, et al. Infectious disease risks associated with occupational exposure: a systematic review of the literature. *Occup Environ Med*. 2012;69:140–146.
191. Bottone EJ. *Bacillus cereus,* a volatile human pathogen. *Clin Microbiol Rev*. 2010;23:382–398.
192. Centers for Disease Control and Prevention. Outbreak of cutaneous *Bacillus cereus* infections among cadets in a university military program—Georgia, August 2004. *MMWR Morb Mortal Wkly Rep*. 2005;54:1233–1235.
201. Mays SR, Bogle MA, Bodey GP. Cutaneous fungal infections in the oncology patient: recognition and management. *Am J Clin Dermatol*. 2006;7:31–43.
205. Chian CA, Arrese JE, Piérard GE. Skin manifestations of *Bartonella* infections. *Int J Dermatol*. 2002;41:461–466.
207. Jemec GB. Clinical practice. Hidradenitis suppurativa. *N Engl J Med*. 2012;366:158–164.
217. Blok JL, van Hattem S, Jonkman MF, et al. Systemic therapy with immunosuppressive agents and retinoids in hidradenitis suppurativa: a systematic review. *Br J Dermatol*. 2013;168:243–252.
220. Nielsen K, Jeppesen M, Simmelsgaard L, et al. Self-inflicted skin diseases: a retrospective analysis of 57 patients with dermatitis artefacta seen in a dermatology department. *Acta Derm Venereol*. 2005;85:512–515.
222. Kingston ME, Mackey D. Skin clues in the diagnosis of life-threatening infections. *Rev Infect Dis*. 1986;8:1–11.
228. Dupin N, Lecuyer H, Carlotti A, et al. Chronic meningococcemia cutaneous lesions involve meningococcal perivascular invasion through the remodeling of endothelial barriers. *Clin Infect Dis*. 2012;54:1162–1165.
237. Marrie TJ. Osler's nodes and Janeway lesions. *Am J Med*. 2008;121:105–106.

268. Chen JL, Fullerton KE, Flynn NM. Necrotizing fasciitis associated with injection drug use. *Clin Infect Dis*. 2001;33:6–15.

279. Bjurlin MA, O'Grady T, Kim DY, et al. Causative pathogens, antibiotic sensitivity, resistance patterns, and severity in a contemporary series of Fournier's gangrene. *Urology*. 2013;81:752–758.

287. Majumdar R, Crum-Cianflone NF. Necrotizing fasciitis due to *Serratia marcescens:* case report and review of the literature. *Infection*. 2016;44:371–377.

288. Hagiya H, Ojima M, Yoshida T, et al. Necrotizing soft tissue infection caused by *Serratia marcescens:* a case report and literature review. *J Infect Chemother*. 2016;22:335–338.

299. Koch C, Hecker A, Grau V, et al. Intravenous immunoglobulin in necrotizing fasciitis: a case report and review of recent literature. *Ann Med Surg (Lond)*. 2015;4:260–263.

302. Abrahamian FM, Goldstein EJ. Microbiology of animal bite wound infections. *Clin Microbiol Rev*. 2011;24:231–246.

311. Thomsen IP, Smith MA, Holland SM, et al. A Comprehensive Approach to the Management of Children and Adults with Chronic Granulomatous Disease. *J Allergy Clin Immunol Pract*. 2016;4:1082–1088.

312. Sillevis Smitt JH, Kuijpers TW. Cutaneous manifestations of primary immunodeficiency. *Curr Opin Pediatr*. 2013;25:492–497.

312a. Grimbacher B, Holland SM, Puck JM. Hyper-IgE syndromes. *Immunol Rev*. 2005;203:244–250.

References

1. Rørtveit S, Rørtveit G. Impetigo in epidemic and nonepidemic phases: an incidence study over 4½ years in a general population. *Br J Dermatol*. 2007;157:100–105.
2. Rørtveit S, Skutlaberg DH, Langeland N, et al. Impetigo in a population over 8.5 years: incidence, fusidic acid resistance and molecular characteristics. *J Antimicrob Chemother*. 2011;66:1360–1364.
3. Ferrieri P, Dajani AS, Wannamaker LW, et al. Natural history of impetigo, I. Site sequence of acquisition and familial patterns of spread of cutaneous streptococci. *J Clin Invest*. 1972;51:2851–2862.
4. Bisno AL, Stevens DL. Streptococcal infections of skin and soft tissues. *N Engl J Med*. 1996;334:240–245.
5. Durupt F, Mayor L, Bes M, et al. Prevalence of *Staphylococcus aureus* toxins and nasal carriage in furuncles and impetigo. *Br J Dermatol*. 2007;157:1161–1167.
6. Dajani AS, Ferrieri P, Wannamaker LW. Natural history of impetigo, II. Etiologic agents and bacterial interactions. *J Clin Invest*. 1972;51:2863–2871.
7. Hochedez P, Canestri A, Lecso M, et al. Skin and soft tissue infections in returning travelers. *Am J Trop Med Hyg*. 2009;80:431–434.
8. Darmstadt GL, Fleckman P, Jonas M, et al. Differentiation of cultured keratinocytes promotes the adherence of *Streptococcus pyogenes*. *J Clin Invest*. 1998;101:128–136.
9. Okada N, Pentland AP, Falk P, et al. M protein and protein F act as important determinations of cell-specific tropism of *Streptococcus pyogenes* in skin tissue. *J Clin Invest*. 1994;94:965–977.
10. Walker MJ, Barnett TC, McArthur JD, et al. Disease manifestations and pathogenic mechanisms of Group A *Streptococcus*. *Clin Microbiol Rev*. 2014;27:264–301.
11. Brouwer S, Barnett TC, Rivera-Hernandez T, et al. *Streptococcus pyogenes* adhesion and colonization. *FEBS Lett*. 2016;590:3739–3757.
12. Bessen DE. Tissue tropisms in group A *Streptococcus:* what virulence factors distinguish pharyngitis from impetigo strains? *Curr Opin Infect Dis*. 2016;29:295–303.
13. Zetola N, Francis JS, Nuermberger EL, et al. Community-acquired methicillin-resistant *Staphylococcus aureus:* an emerging threat. *Lancet Infect Dis*. 2005;5:275–286.
14. Dillon HC. Post-streptococcal glomerulonephritis following pyoderma. *Rev Infect Dis*. 1979;1:935–945.
15. Bessen DE, McGregor KF, Whatmore AM. Relationships between emm and multilocus sequence types within a global collection of *Streptococcus pyogenes*. *BMC Microbiol*. 2008;8:59–70.
16. Burge SM, Ryan TJ. Acute palmoplantar pustulosis. *Br J Dermatol*. 1985;113:77–83.
17. McLaughlin J, Low JC. Primary cutaneous listeriosis in adults: an occupational disease of veterinarians and farmers. *Vet Rec*. 1994;135:615–617.
18. Brown J, Shriner DL, Schwartz RA, et al. Impetigo: an update. *Int J Dermatol*. 2003;42:251–255.
19. Bowen AC, Lilliebridge RA, Tong SY, et al. Is *Streptococcus pyogenes* resistant or susceptible to trimethoprim-sulfamethoxazole? *J Clin Microbiol*. 2012;50:4067–4072.
20. Bowen AC, Carapetis JR, Currie BJ, et al. Sulfamethoxazole-trimethoprim (cotrimoxazole) for skin and soft tissue infections including impetigo, cellulitis, and abscess. *Open Forum Infect Dis*. 2017;4:ofx232.
21. Stevens DL, Bisno AL, Chambers HF, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the infectious diseases society of America. *Clin Infect Dis*. 2014;59:147–159. See also *Clin Infect Dis*. 2014;59:e1–e52.
22. Bangert S, Levy M, Hebert AA. Bacterial resistance and impetigo treatment trends: a review. *Pediatr Dermatol*. 2012;29:243–248.
23. Williamson DA, Carter GP, Howden BP. Current and emerging topical antibacterials and antiseptics: agents, action, and resistance patterns. *Clin Microbiol Rev*. 2017;30:827–860.
24. Koning S, van der Wouden JC, Chosidow O, et al. Efficacy and safety of retapamulin ointment as treatment of impetigo: randomized double-blind multicentre placebo-controlled trial. *Br J Dermatol*. 2008;158:1077–1082.
25. Bukowski M, Wladyka B, Dubin G. Exfoliative toxins of *Staphylococcus aureus*. *Toxins (Basel)*. 2010;2:1148–1165.
26. Stanley JR, Amagai M. Pemphigus, bullous impetigo, and the staphylococcal scalded-skin syndrome. *N Engl J Med*. 2006;355:1800–1810.
27. Hubiche T, Bes M, Roudiere L, et al. Mild staphylococcal scalded skin syndrome: an underdiagnosed clinical disorder. *Br J Dermatol*. 2012;166:213–215.
28. Knox BL, Petska HW, DeMuri GP, et al. Staphylococcal infection mimicking child abuse: what is the differential diagnosis and appropriate evaluation? *Pediatr Emerg Care*. 2011;27:547–549.
29. Murray RJ. Recognition and management of *Staphylococcus aureus* toxin-mediated disease. *Intern Med J*. 2005;35(suppl 2):S106–S119.
30. Curran JP, Al-Salihi FL. Neonatal staphylococcal scalded skin syndrome: massive outbreak due to an unusual phage type. *Pediatrics*. 1980;66:285–290.
31. Lina G, Gillet Y, Vandenesch F, et al. Toxin involvement in staphylococcal scalded skin syndrome. *Clin Infect Dis*. 1997;25:1369–1373.
32. Low DE. Toxic shock syndrome: major advances in pathogenesis, but not treatment. *Crit Care Clin*. 2013;29:651–675.
33. Lappin E, Ferguson AJ. Gram-positive toxic shock syndromes. *Lancet Infect Dis*. 2009;9:281–290.
34. Levy AL, Simpson G, Skinner RB Jr. Medical pearl: circle of desquamation—a clue to the diagnosis of folliculitis and furunculosis caused by *Staphylococcus aureus*. *J Am Acad Dermatol*. 2006;55:1079–1080.
35. Yu Y, Cheng AS, Wang L, et al. Hot tub folliculitis or hot hand-foot syndrome caused by *Pseudomonas aeruginosa*. *J Am Acad Dermatol*. 2007;57:596–600.
36. El Baze P, Thyss A, Caldini C, et al. *Pseudomonas aeruginosa* 0-11 folliculitis: development into ecthyma gangrenosum in immunosuppressed patients. *Arch Dermatol*. 1985;121:873–876.
37. Stähelin-Massik J, Gnehm HE, Itin PH. *Pseudomonas* folliculitis in a young child. *Pediatr Infect Dis J*. 2000;19:362–363.
38. Neubert U, Jansen H, Plewig G. Bacteriologic and immunologic aspects of gram-negative folliculitis: a study of 46 patients. *Int J Dermatol*. 1999;38:270–274.
39. Durdu M, Güran M, Kandemir H, et al. Clinical and Laboratory Features of Six Cases of Candida and Dermatophyte Folliculitis and a Review of Published Studies. *Mycopathologia*. 2016;181:97–105.
40. Archer-Dubon C, Icaza-Chivez ME, Orozco-Topete R. An epidemic outbreak of *Malassezia* folliculitis in three adult patients in an intensive care unit: a previously unrecognized nosocomial infection. *Int J Dermatol*. 1999;38:453–456.
41. Tragiannidis A, Bisping G, Koehler G, et al. Minireview: *Malassezia* infections in immunocompromised patients. *Mycoses*. 2010;53:187–195.
42. Ayers K, Sweeney SM, Wiss K. *Pityrosporum* folliculitis: diagnosis and management in 6 female adolescents with acne vulgaris. *Arch Pediatr Adolesc Med*. 2005;159:64–67.
43. Campanelli A, Marazza G, Stucki L, et al. Fulminant herpetic sycosis: atypical presentation of primary herpetic infection. *Dermatology*. 2004;208:284–286.
44. Talbot TR, Bredenberg HK, Smith M, et al. Focal and generalized folliculitis following smallpox vaccination among vaccinia-naive recipients. *JAMA*. 2003;289:3290–3294.
45. Sanfilippo AM, English JC 3rd. Resistant scalp folliculitis secondary to *Demodex* infestation. *Cutis*. 2005;76:321–324.
46. Nervi SJ, Schwartz RA, Dmochowski M. Eosinophilic pustular folliculitis: a 40-year retrospect. *J Am Acad Dermatol*. 2006;55:285–289.
47. Okuyama R, Masu T, Kumasaka N, et al. Amicrobial pustulosis of the folds affecting a young male without any accompanying autoimmune diseases. *Dermatology*. 2008;217:121–123.
48. Lee HY, Pelivani N, Beltraminelli H, et al. Amicrobial pustulosis-like rash in a patient with Crohn's disease under anti-TNF-alpha blocker. *Dermatology*. 2011;222:304–310.
49. Sladden MJ, Johnston GA. More common skin infections in children. *BMJ*. 2005;330:1194–1198.
50. Natsis NE, Cohen PR. Coagulase-negative *Staphylococcus* skin and soft tissue infections. *Am J Clin Dermatol*. 2018;19:671–677.
51. Demos M, McLeod MP, Nouri K. Recurrent furunculosis: a review of the literature. *Br J Dermatol*. 2012;167:725–732.
52. Moellering RC Jr, Abbott GF, Ferraro MJ. Case records of the Massachusetts General Hospital. Case 2-2011. A 30-year-old woman with shock after treatment of a furuncle. *N Engl J Med*. 2011;364:266–275.
53. Baba-Moussa L, Sina H, Scheftel JM, et al. Staphylococcal Panton-Valentine leucocidin as a major virulence factor associated to furuncles. *PLoS ONE*. 2011;6:e25716.
54. Johnston SL. Clinical immunology review series: an approach to the patient with recurrent superficial abscesses. *Clin Exp Immunol*. 2008;152:397–405.
55. Demos M, McLeod MP, Nouri K. Recurrent furunculosis: a review of the literature. *Br J Dermatol*. 2012;167:725–732.
56. Huang JT, Abrams M, Tlougan B, et al. Treatment of *Staphylococcus aureus* colonization in atopic dermatitis decreases disease severity. *Pediatrics*. 2009;123:e808–e814.
57. Ammerlaan HS, Kluytmans JA, Wertheim HF, et al. Eradication of methicillin-resistant *Staphylococcus aureus* carriage: a systematic review. *Clin Infect Dis*. 2009;48:922–930.
58. Simor AE, Phillips E, McGeer A, et al. Randomized controlled trial of chlorhexidine gluconate for washing, intranasal mupirocin, and rifampin and doxycycline versus no treatment for the eradication of methicillin-resistant *Staphylococcus aureus* colonization. *Clin Infect Dis*. 2007;44:178–185.
59. Fritz SA, Hogan PG, Camins BC, et al. Mupirocin and chlorhexidine resistance in *Staphylococcus aureus* in patients with community-onset skin and soft tissue infections. *Antimicrob Agents Chemother*. 2013;57:559–568.
60. Sniezek PJ, Graham BS, Busch HB, et al. Rapidly growing mycobacterial infections after pedicures. *Arch Dermatol*. 2003;139:629–634.
61. Wasserzug O, Valinsky L, Klement E, et al. A cluster of ecthyma outbreaks caused by a single clone of invasive and highly infective *Streptococcus pyogenes*. *Clin Infect Dis*. 2009;48:1213–1219.
62. Hewitt WD, Farrar WE. Case report: bacteremia and ecthyma caused by *Streptococcus pyogenes* in a patient with acquired immunodeficiency syndrome. *Am J Med Sci*. 1988;295:52–54.
63. Vaiman M, Lazarovitch T, Heller L, et al. Ecthyma gangrenosum and ecthyma-like lesions: review article. *Eur J Clin Microbiol Infect Dis*. 2015;34:633–639.
64. Hicks CW, Sweeney DA, Cui X, et al. An overview of anthrax infection including the recently identified form of disease in injection drug users. *Intensive Care Med*. 2012;38:1092–1104.
65. Centers for Disease Control and Prevention (CDC). Gastrointestinal anthrax after an animal-hide drumming event—New Hampshire and Massachusetts, 2009. *MMWR Morb Mortal Wkly Rep*. 2010;59:872–877.
66. Inglesby TV, O'Toole T, Henderson DA, et al. Anthrax as a biological weapon 2002: updated recommendations for management. *JAMA*. 2002;287:2236–2252.
67. Smego RA, Gebrain B, Desmangels G. Cutaneous manifestations of anthrax in rural Haiti. *Clin Infect Dis*. 1998;26:97–101.
68. Swartz MN. Recognition and treatment of anthrax: an update. *N Engl J Med*. 2001;345:1621–1626.
69. Moayeri M, Leppla SH, Vrentas C, et al. Anthrax pathogenesis. *Annu Rev Microbiol*. 2015;69:185–208.
70. Centers for Disease Control and Prevention. Update: investigation of bioterrorism-related anthrax and interim guidelines for exposure management and antimicrobial therapy, October 2001. *MMWR Morb Mortal Wkly Rep*. 2001;50:909–919.
71. Greig SL. Obiltoxaximab: first global approval. *Drugs*. 2016;76:823–830.
72. Bernard P, Bedame C, Mounier M, et al. Streptococcal cause of erysipelas and cellulitis in adults. *Arch Dermatol*. 1989;125:779–782.
73. Gunderson CG, Martinello RA. A systematic review of bacteremias in cellulitis and erysipelas. *J Infect*. 2012;64:148–155.
74. Bläckberg A, Trell K, Rasmussen M. Erysipelas, a large retrospective study of aetiology and clinical presentation. *BMC Infect Dis*. 2015;15:402.
75. Jorup-Ronstrom C. Epidemiological, bacteriological and complicating features of erysipelas. *Scand J Infect Dis*. 1986;18:519–524.
76. Damstra RJ, van Steensel MA, Boomsma JH, et al. Erysipelas as a sign of subclinical primary lymphoedema: a prospective quantitative scintigraphic study of 40 patients with unilateral erysipelas of the leg. *Br J Dermatol*. 2008;158:1210–1215.
77. Eriksson BKG. Anal colonization of group G β-hemolytic streptococci in relapsing erysipelas of the lower extremity. *Clin Infect Dis*. 1999;29:1319–1320.
78. Del Giudice P, van der Mee-Marquet N, David-Rubin F, et al. Severe relapsing erysipelas associated with chronic *Streptococcus agalactiae* vaginal colonization. *Clin Infect Dis*. 2006;43:e67–e70.
79. Guberman D, Gilead LT, Zlotogorski A, et al. Bullous erysipelas: a retrospective study of 26 patients. *J Am Acad Dermatol*. 1999;41:733–737.
80. Krasagakis K, Samonis G, Maniatakis P, et al. Bullous erysipelas: clinical presentation, staphylococcal involvement and methicillin resistance. *Dermatology*. 2006;212:31–35.
81. Aydin F, Ozcelik C, Akpolat I, et al. Erysipelas-like erythema with familial Mediterranean fever. *J Dermatol*. 2011;38:513–515.
82. Kerstens PJ, Endtz HP, Meis JF, et al. Erysipelas-like lesions associated with *Campylobacter jejuni* septicemia in patients with hypogammaglobulinemia. *Eur J Clin Microbiol Infect Dis*. 1992;11:842–847.

83. DeMuri GP, Sterkel AK, Kubica PA, et al. Macrolide and clindamycin resistance in group A streptococci isolated from children with pharyngitis. *Pediatr Infect Dis J*. 2017;36:342–344.
84. Leclerc S, Teixeira A, Mahé E, et al. Recurrent erysipelas: 47 cases. *Dermatology*. 2007;214:52–57.
85. Thomas KS, Crook AM, Nunn AJ, et al. Penicillin to prevent recurrent leg cellulitis. *N Engl J Med*. 2013; 368:1695–1703.
86. Oh CC, Ko HC, Lee HY, et al. Antibiotic prophylaxis for preventing recurrent cellulitis: a systematic review and meta-analysis. *J Infect*. 2014;69:26–34.
87. Baddour LM, Bisno AL. Recurrent cellulitis after saphenous venectomy for coronary bypass surgery. *Ann Intern Med*. 1982;97:493–496.
88. Andreasen JJ, Nekrasas V, Dethlefsen C. Endoscopic vs open saphenous vein harvest for coronary artery bypass grafting: a prospective randomized trial. *Eur J Cardiothorac Surg*. 2008;34:384–389.
89. Zenati MA, Bhatt DL, Bakaeen FG, et al. Randomized trial of endoscopic or open vein-graft harvesting for coronary-artery bypass. *N Engl J Med*. 2019;380:132–141.
90. Chmel H, Hamdy M. Recurrent streptococcal cellulitis complicating radical hysterectomy and radiation therapy. *Obstet Gynecol*. 1984;63:862–864.
91. Simon MS, Cody RL. Cellulitis after axillary lymph node dissection for carcinoma of the breast. *Am J Med*. 1992;93:543–548.
92. Mertz KR, Baddour LM, Bell JL, et al. Breast cellulitis following breast conservation therapy: a novel complication of medical progress. *Clin Infect Dis*. 1998;26:481–486.
93. Raff AB, Kroshinsky D. Cellulitis: a review. *JAMA*. 2016;316:325–337.
94. Collazos J, de la Fuente B, García A, et al. Cellulitis in adult patients: a large, multicenter, observational, prospective study of 606 episodes and analysis of the factors related to the response to treatment. *PLoS ONE*. 2018;13:e0204036.
95. Tay EY, Fook-Chong S, Oh CC, et al. Cellulitis Recurrence Score: a tool for predicting recurrence of lower limb cellulitis. *J Am Acad Dermatol*. 2015;72:140–145.
96. Baroni A, Buommino E, Piccolo V, et al. Alterations of skin innate immunity in lymphedematous limbs: correlations with opportunistic diseases. *Clin Dermatol*. 2014;32:592–598.
97. Carlson JA. Lymphedema and subclinical lymphostasis (microlymphedema) facilitate cutaneous infection, inflammatory dermatoses, and neoplasia: a locus minoris resistentiae. *Clin Dermatol*. 2014;32:599–615.
98. Scaglioni MF, Fontein DBY, Arvanitakis M, et al. Systematic review of lymphovenous anastomosis (LVA) for the treatment of lymphedema. *Microsurgery*. 2017;37:947–953.
99. Ellison RT III, McGregor JA. Recurrent postcoital lower extremity streptococcal erythroderma in women: streptococcal-sex syndrome. *JAMA*. 1987;257: 3260–3262.
100. Barzilae A, Choen HA. Isolation of group A streptococci from children with perianal cellulitis and from their siblings. *Pediatr Infect Dis J*. 1998;17:358–360.
101. Clegg HW, Giftos PM, Anderson WE, et al. Clinical perineal streptococcal infection in children: epidemiologic features, low symptomatic recurrence rate after treatment, and risk factors for recurrence. *J Pediatr*. 2015;167:687–693.
102. Swartz MN. Cellulitis. *N Engl J Med*. 2004;350:904–912.
103. Givner LB, Mason EO Jr, Barson WJ, et al. Pneumococcal facial cellulitis in children. *Pediatrics*. 2000;106:E61.
104. Capdevila O, Grau I, Vadillo M, et al. Bacteremic pneumococcal cellulitis compared with bacteremic cellulitis caused by *Staphylococcus aureus* and *Streptococcus pyogenes*. *Eur J Clin Microbiol Infect Dis*. 2003;22:337–341.
105. Badaoui A, Reygagne P, Cavelier-Balloy B, et al. Dissecting cellulitis of the scalp: a retrospective study of 51 patients and review of literature. *Br J Dermatol*. 2016;174:421–423.
106. Chira S, Miller LG. Staphylococcus aureus is the most common identified cause of cellulitis: a systematic review. *Epidemiol Infect*. 2010;138:313–317.
107. Lipsky BA, Berendt AR, Cornia PB, et al. 2012 Infectious Diseases Society of America clinical practice guideline for the diagnosis and treatment of diabetic foot infections. *Clin Infect Dis*. 2012;54:e132–e173.
108. Kitamura T, Kawamura Y, Ohkusu K, et al. *Helicobacter cinaedi* cellulitis and bacteremia in immunocompetent hosts after orthopedic surgery. *J Clin Microbiol*. 2007;45:31–38.
109. Shimizu S, Shimizu H. Cutaneous manifestations of Helicobacter cinaedi: a review. *Br J Dermatol*. 2016; 175:62–68.
110. Woo PC, Lum PML, Wong SSY, et al. Cellulitis complicating lymphoedema. *Eur J Clin Microbiol Infect Dis*. 2000;19:294–297.
111. Brooke CJ, Riley TV. *Erysipelothrix rhusiopathiae:* bacteriology, epidemiology and clinical manifestations of an occupational pathogen. *J Med Microbiol*. 1999;48:789–799.
112. Lewin MR, Knott P, Lo M. Seal finger. *Lancet*. 2004;364:448.
113. Westley BP, Horazdovsky RD, Michaels DL, et al. Identification of a Novel Mycoplasma Species in a Patient With Septic Arthritis of the Hip and Seal Finger. *Clin Infect Dis*. 2016;62:491–493.
114. Gold WL, Salit IE. *Aeromonas hydrophila* infections of skin and soft tissue: report of 11 cases and review. *Clin Infect Dis*. 1993;16:69–74.
115. Finkelstein R, Oren I. Soft tissue infections caused by marine bacterial pathogens: epidemiology, diagnosis, and management. *Curr Infect Dis Rep*. 2011;13:470–477.
116. Dechet AM, Yu PA, Koram N, et al. Nonfoodborne *Vibrio* infections: an important cause of morbidity and mortality in the United States, 1997-2006. *Clin Infect Dis*. 2008;46:970–976.
117. Chuang Y-C, Yuan C-Y, Liu C-Y, et al. *Vibrio vulnificus* infection in Taiwan: report of 28 cases and review of clinical manifestations and treatment. *Clin Infect Dis*. 1992;15:271–276.
118. Zhao H, Xu L, Dong H, et al. Correlations between Clinical Features and Mortality in Patients with Vibrio vulnificus Infection. *PLoS ONE*. 2015;10:e0136019.
119. Maraki S, Christidou A, Anastasaki M, et al. Non-O1, non-O139 Vibrio cholerae bacteremic skin and soft tissue infections. *Infect Dis (Lond)*. 2016;48:171–176.
120. Kielbauch JA, Tauxe RV, Baker CN, et al. *Helicobacter cinaedi*–associated bacteremia and cellulitis in immunocompromised patients. *Ann Intern Med*. 1994;121:90–93.
121. Horrevorts AM, Huysmans FTM, Koopman RJJ, et al. Cellulitis as first clinical presentation of disseminated cryptococcosis in renal transplant recipients. *Scand J Infect Dis*. 1994;26:623–626.
122. Nucci M, Anaissie E. *Fusarium* infections in immunocompromised patients. *Clin Microbiol Rev*. 2007;20:695–704.
123. Waldor MK, Wilson B, Swartz M. Cellulitis caused by *Legionella pneumophila*. *Clin Infect Dis*. 1993;16:51–53.
124. Kilborn JA, Manz LA, O'Brien M, et al. Necrotizing cellulitis caused by *Legionella micdadei*. *Am J Med*. 1992;92:104–106.
125. Sleiman JN, D'Angelo A, Hammerschlag MR. Spontaneous *Escherichia coli* cellulitis in a child with nephrotic syndrome. *Pediatr Infect Dis J*. 2007;26:266–267.
126. Sunder S, Haguenoer E, Bouvet D, et al. Life-threatening *Escherichia coli* cellulitis in patients with haematological malignancies. *J Med Microbiol*. 2012;61:1324–1327.
127. Falagas ME, Vergidis PI. Narrative review: diseases that masquerade as infectious cellulitis. *Ann Intern Med*. 2005;142:47–55.
128. Blumberg G, Long B, Koyfman A. Clinical mimics: an emergency medicine-focused review of cellulitis mimics. *J Emerg Med*. 2017;53:475–484.
129. Prentice O, Fernandez WG, Luyber TJ, et al. Stonefish envenomation. *Am J Emerg Med*. 2008;26:972.e1–972.e2.
130. Hornbeak KB, Auerbach PS. Marine envenomation. *Emerg Med Clin North Am*. 2017;35:321–337.
131. Majeed HA, Quabazard Z, Hijasi Z, et al. The cutaneous manifestations in children with familial Mediterranean fever (recurrent hereditary polyserositis): a six-year study. *QJM*. 1990;75:607–616.
132. Abbas O, Kibbi AG, Rubeiz N. Sweet's syndrome: retrospective study of clinical and histologic features of 44 cases from a tertiary care center. *Int J Dermatol*. 2010;49:1244–1249.
133. Nelson CA, Stephen S, Ashchyan HJ, et al. Neutrophilic dermatoses: pathogenesis, Sweet syndrome, neutrophilic eccrine hidradenitis, and Behçet disease. *J Am Acad Dermatol*. 2018;79:987–1006.
134. Crum NF, Higginbottom PA, Fehl FC, et al. Sweet's syndrome masquerading as facial cellulitis. *Cutis*. 2003;71:469–472.
135. Sheard RM, Pandey KR, Barnes ND, et al. Kawasaki disease presenting as orbital cellulitis. *J Pediatr Ophthalmol Strabismus*. 2000;37:123–125.
136. Green WH, Yosipovitch G, Pichardo RO. Recurrent, pruritic dermal plaques and bullae. Diagnosis: eosinophilic cellulitis (Wells syndrome). *Arch Dermatol*. 2007;143:791–796.
137. Räßler F, Lukács J, Elsner P. Treatment of eosinophilic cellulitis (Wells syndrome) - a systematic review. *J Eur Acad Dermatol Venereol*. 2016;30:1465–1479.
138. Faber K, Schroeder L, Thill M-P, et al. Carcinoma erysipeloides of the neck. *Lancet*. 2002;359:1025.
139. Gunderson CG. Cellulitis: definition, etiology, and clinical features. *Am J Med*. 2011;124:1113–1122.
140. Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children. *Clin Infect Dis*. 2011;52:e18–e55.
141. Busch BA, Ahern MT, Topinka M, et al. Eschar with cellulitis as a clinical predictor in community-acquired MRSA skin abscess. *J Emerg Med*. 2010;38:563.
142. File TM Jr, Wilcox MH, Stein GE. Summary of ceftaroline fosamil clinical trial studies and clinical safety. *Clin Infect Dis*. 2012;55(suppl 3):S173–S180.
143. McClain SL, Bohan JG, Stevens DL. Advances in the medical management of skin and soft tissue infections. *BMJ*. 2016;355:i6004.
144. Khawcharoenporn T, Tice A. Empiric outpatient therapy with trimethoprim-sulfamethoxazole, cephalexin, or clindamycin for cellulitis. *Am J Med*. 2010;123:942–950.
145. Pallin DJ, Binder WD, Allen MB, et al. Clinical trial: comparative effectiveness of cephalexin plus trimethoprim-sulfamethoxazole versus cephalexin alone for treatment of uncomplicated cellulitis: a randomized controlled trial. *Clin Infect Dis*. 2013;56:1754–1762.
146. Miller LG, Daum RS, Creech CB, et al. Clindamycin versus trimethoprim-sulfamethoxazole for uncomplicated skin infections. *N Engl J Med*. 2015;372:1093–1103.
147. Wessels MR. Choosing an antibiotic for skin infections. *N Engl J Med*. 2015;372:1164–1165.
148. Talan DA, Mower WR, Krishnadasan A, et al. Trimethoprim-sulfamethoxazole versus placebo for uncomplicated skin abscess. *N Engl J Med*. 2016;374:823–832.
149. Rockson SG. Diagnosis and management of lymphatic vascular disease. *J Am Coll Cardiol*. 2008;52:799–806.
150. Thomas KS, Crook AM, Nunn AJ, et al; U.K. Dermatology Clinical Trials Network's PATCH I Trial Team. Penicillin to prevent recurrent leg cellulitis. *N Engl J Med*. 2013;368:1695–1703.
151. Eiset AH, Wejse C. Review of infectious diseases in refugees and asylum seekers-current status and going forward. *Public Health Rev*. 2017;38:22.
152. Rahman MR, Islam K. Massive diphtheria outbreak among Rohingya refugees: lessons learnt. *J Travel Med*. 2019;26.
153. Lowe CF, Bernard KA, Romney MG. Cutaneous diphtheria in the urban poor population of Vancouver, British Columbia, Canada: a 10-year review. *J Clin Microbiol*. 2011;49:2664–2666.
154. Moore LSP, Leslie A, Meltzer M, et al. Corynebacterium ulcerans cutaneous diphtheria. *Lancet Infect Dis*. 2015;15:1100–1107.
155. Belsey MA, Sinclair M, Roder MR, et al. *Corynebacterium diphtheriae* skin infections in Alabama and Louisiana: a factor in the epidemiology of diphtheria. *N Engl J Med*. 1969;280:135–141.
156. Gruner E, Opravil M, Altwegg M, et al. Nontoxigenic *Corynebacterium diphtheriae* isolated from intravenous drug users. *Clin Infect Dis*. 1994;18:94–96.
157. Golaz A, Hardy IR, Strebel P, et al. Epidemic diphtheria in the newly independent states of the former Soviet Union: implications for diphtheria control in the United States. *J Infect Dis*. 2000;181(suppl 1):S237–S243.
158. Barker FG, Leppard BJ, Seal DV. Streptococcal necrotizing fasciitis: comparison between histological and clinical features. *J Clin Pathol*. 1987;40:335–341.
159. Aitken DR, Mackett MC, Smith LL. The changing pattern of hemolytic streptococcal gangrene. *Arch Surg*. 1982;117:561–567.
160. Stevens DL. Streptococcal toxic-shock syndrome: spectrum of disease, pathogenesis, and new concepts in treatment. *Emerg Infect Dis*. 1995;1:69–78.
161. Strasberg SM, Silver MS. Hemolytic streptococcus gangrene: an uncommon but frequently fatal infection in the antibiotic era. *Am J Surg*. 1968;115:763–768.
162. Meleney FL. Bacterial synergism in disease processes with a confirmation of the synergistic bacterial etiology of a certain type of progressive gangrene of the abdominal wall. *Ann Surg*. 1931;94:961–981.
163. Davson J, Jones DM, Turner L. Diagnosis of Meleney's synergistic gangrene. *Br J Surg*. 1988;75:267–271.
164. Turner L, Jones DM, Davson J. Cutaneous amoebiasis: case report. *BMJ*. 1985;291:635–636.
165. Boyd AS, Wiser B, Sams HH, et al. Gangrenous cutaneous mucormycosis in a child with a solid organ transplant: a case report and review of the literature. *Pediatr Dermatol*. 2003;20:411–415.
166. Antoniadou A. Outbreaks of zygomycosis in hospitals. *Clin Microbiol Infect*. 2009;15(suppl 5):55–59.
167. Wilson CB, Siber GR, O'Brien TF, et al. Phycomycotic gangrenous cellulitis. A report of two cases and a review of the literature. *Arch Surg*. 1976;111:532–538.

168. Gomes MZ, Lewis RE, Kontoyiannis DP. Mucormycosis caused by unusual mucormycetes, non-*Rhizopus, -Mucor,* and *-Lichtheimia* species. *Clin Microbiol Rev*. 2011;24:411–445.
169. Rogers NM, Teubner DJ, Coates PT. Calcific uremic arteriolopathy: advances in pathogenesis and treatment. *Semin Dial*. 2007;20:150–157.
170. Nigwekar SU, Thadhani R, Brandenburg VM. Calciphylaxis. *N Engl J Med*. 2018;378:1704–1714.
171. Moran GJ, Krishnadasan A, Gorwitz RJ, et al; EMERGEncy ID Net Study Group. Methicillin-resistant *S. aureus* infections among patients in the emergency department. *N Engl J Med*. 2006;355:666–674.
172. Coyle EA, Cha R, Ryback MJ. Influences of linezolid, penicillin, and clindamycin alone and in combination, on streptococcal pyrogenic exotoxin A release. *Antimicrob Agents Chemother*. 2003;47:1752–1755.
173. Miller SD, David-Bajar K. Images in clinical medicine. a brilliant case of erythrasma. *N Engl J Med*. 2004;351:1666.
174. Turk BG, Turkmen M, Aytimur D. Antibiotic susceptibility of *Corynebacterium minutissimum* isolated from lesions of Turkish patients with erythrasma. *J Am Acad Dermatol*. 2011;65:1230–1231.
175. Takama H, Tamada Y, Yano K, et al. Pitted keratolysis: clinical manifestations in 53 cases. *Br J Dermatol*. 1997;137:282–285.
176. Bowler PG, Duerden BI, Armstrong DG. Wound microbiology and associated approaches to wound management. *Clin Microbiol Rev*. 2001;8:244–269.
177. Khanolkar MP, Bain SC, Stephens JW. The diabetic foot. *QJM*. 2008;101:685–695.
178. Ikoloudi M, Eleftheriadou I, Tentolouris A, et al. Diabetic foot infections: update on management. *Curr Infect Dis Rep*. 2018;20:40.
179. Gerding DM. Foot infections in diabetic patients: role of anaerobes. *Clin Infect Dis*. 1995;20(suppl 2):S283–S288.
180. Eleftheriadou I, Tentolouris N, Argiana V, et al. Methicillin-resistant *Staphylococcus aureus* in diabetic foot infections. *Drugs*. 2010;70:1785–1797.
181. Peters EJ, Lipsky BA, Aragón-Sánchez J, et al. Interventions in the management of infection in the foot in diabetes: a systematic review. *Diabetes Metab Res Rev*. 2016;32(suppl 1):145–153.
182. Janda JM, Abbott SL, Brenden RA. Overview of the etiology of wound infections with particular emphasis on community-acquired illnesses. *Eur J Clin Microbiol Infect Dis*. 1997;16:189–201.
183. Haagsma JA, Tariq L, Heederik DJ, et al. Infectious disease risks associated with occupational exposure: a systematic review of the literature. *Occup Environ Med*. 2012;69:140–146.
184. Kyerematen-Amoah E, Nowell J, Lutty A, et al. Laceration injuries and infections among workers in the poultry processing and pork meatpacking industries. *Am J Ind Med*. 2014;57:669–682.
185. Yaffe MA, Kaplan FT. Agricultural injuries to the hand and upper extremity. *J Am Acad Orthop Surg*. 2014;22:605–613.
186. Weinstein MR, Litt M, Kertess DA, et al. Invasive infections due to a fish pathogen, *Streptococcus iniae*. *N Engl J Med*. 1997;337:589–594.
187. Eiland LS, Salazar ML. Polymicrobial catfish spine infection in a child. *Pediatr Infect Dis J*. 2006;25:281–282.
188. Kaar CRJ, Nakanishi AK. Recreational and commercial catfishing injuries: a review of the literature. *Wilderness Environ Med*. 2017;28:348–354.
189. Diaz JH, Lopez FA. Skin, soft tissue and systemic bacterial infections following aquatic injuries and exposures. *Am J Med Sci*. 2015;349:269–275.
190. Burke VE, Lopez FA. Approach to skin and soft tissue infections in non-HIV immunocompromised hosts. *Curr Opin Infect Dis*. 2017;30:354–363.
191. Bottone EJ. *Bacillus cereus,* a volatile human pathogen. *Clin Microbiol Rev*. 2010;23:382–398.
192. Centers for Disease Control and Prevention. Outbreak of cutaneous *Bacillus cereus* infections among cadets in a university military program—Georgia, August 2004. *MMWR Morb Mortal Wkly Rep*. 2005;54:1233–1235.
193. Hussein MR. Mucocutaneous Splendore-Hoeppli phenomenon. *J Cutan Pathol*. 2008;35:979–988.
194. Gavin PJ, Das L, Chadwick EG, et al. Botryomycosis in a child with acquired immunodeficiency syndrome. *Pediatr Infect Dis J*. 2000;19:900–901.
195. Pettit CJ, Mazurek K, Kaffenberger B. Cutaneous manifestations of infections in solid organ transplant recipients. *Curr Infect Dis Rep*. 2018;20:16.
196. Tortorano AM, Richardson M, Roilides E, et al. ESCMID and ECMM joint guidelines on diagnosis and management of hyalohyphomycosis: Fusarium spp., Scedosporium spp. and others. *Clin Microbiol Infect*. 2014;20(suppl 3):27–46.
197. Guégan S, Garcia-Hermoso D, Sitbon K, et al. Ten-Year Experience of Cutaneous and/or Subcutaneous Infections Due to Coelomycetes in France. *Open Forum Infect Dis*. 2016;3:ofw106.
198. Tseng HC, Chen CB, Ho JC, et al. Clinicopathological features and course of cutaneous protothecosis. *J Eur Acad Dermatol Venereol*. 2018;32:1575–1583.
199. Ayoade F, Mada P, Joel Chandranesan AS, et al. Sporotrichoid Skin Infection Caused by *Nocardia brasiliensis* in a Kidney Transplant Patient. *Diseases*. 2018;6:pii: E68.
200. Marcoux D, Jafarian F, Joncas V, et al. Deep cutaneous fungal infections in immunocompromised children. *J Am Acad Dermatol*. 2009;61:857–864.
201. Mays SR, Bogle MA, Bodey GP. Cutaneous fungal infections in the oncology patient: recognition and management. *Am J Clin Dermatol*. 2006;7:31–43.
202. Bernardeschi C, Foulet F, Ingen-Housz-Oro S, et al. Cutaneous invasive aspergillosis: retrospective multicenter study of the French invasive-aspergillosis registry and literature review. *Medicine (Baltimore)*. 2015;94:e1018.
203. Rouzaud C, Chosidow O, Brocard A, et al. Severe dermatophytosis in solid organ transplant recipients: a French retrospective series and literature review. *Transpl Infect Dis*. 2018;20.
204. Karakas M, Aksungur VL, Homan S, et al. Bacillary angiomatosis on a region of burned skin in an immunocompetent patient. *Br J Dermatol*. 2000;143:609–661.
205. Chian CA, Arrese JE, Piérard GE. Skin manifestations of *Bartonella* infections. *Int J Dermatol*. 2002;41:461–466.
206. Murillo O, Mimbrera D, Petit A, et al. Fatal bacillary angiomatosis mimicking an infiltrative vascular tumour in the immune restoration phase of an HIV-infected patient. *Antivir Ther*. 2012;17:405–407.
207. Jemec GB. Clinical practice. Hidradenitis suppurativa. *N Engl J Med*. 2012;366:158–164.
208. Cosmatos I, Matcho A, Weinstein R, et al. Analysis of patient claims data to determine the prevalence of hidradenitis suppurativa in the United States. *Am Acad Dermatol*. 2013;68:412–419.
209. Fismen S, Ingvarsson G, Moseng D, et al. A clinical-pathological review of hidradenitis suppurativa: using immunohistochemistry one disease becomes two. *APMIS*. 2012;120:433–440.
210. Saunte DML, Jemec GBE. Hidradenitis suppurativa: advances in diagnosis and treatment. *JAMA*. 2017;318:2019–2032.
211. Ergun T. Hidradenitis suppurativa and the metabolic syndrome. *Clin Dermatol*. 2018;36:41–47.
212. Bui TL, Silva-Hirschberg C, Torres J, et al. Hidradenitis suppurativa and diabetes mellitus: a systematic review and meta-analysis. *J Am Acad Dermatol*. 2018;78:395–402.
213. Dréno B, Khammari A, Brocard A, et al. Hidradenitis suppurativa: the role of deficient cutaneous innate immunity. *Arch Dermatol*. 2012;148:182–186.
214. Lim DT, James NM, Hassan S, et al. Spondyloarthritis associated with acne conglobata, hidradenitis suppurativa and dissecting cellulitis of the scalp: a review with illustrative cases. *Curr Rheumatol Rep*. 2013;15:346.
215. Yazdanyar S, Jemec GB. Hidradenitis suppurativa: a review of cause and treatment. *Curr Opin Infect Dis*. 2011;24:118–123.
216. van Straalen KR, Schneider-Burrus S, Prens EP. Current and future treatment of hidradenitis suppurativa. *Br J Dermatol*. 2018;[Epub ahead of print].
217. Blok JL, van Hattem S, Jonkman MF, et al. Systemic therapy with immunosuppressive agents and retinoids in hidradenitis suppurativa: a systematic review. *Br J Dermatol*. 2013;168:243–252.
218. Brook I. The role of anaerobic bacteria in cutaneous and soft tissue abscesses and infected cysts. *Anaerobe*. 2007;13:171–177.
219. Bosman WM, Brekelmans W, Verduijn PS, et al. Necrotising fasciitis due to an infected sebaceous cyst. *BMJ Case Rep*. 2014;2014:pii: bcr2013201905.
220. Nielsen K, Jeppesen M, Simmelsgaard L, et al. Self-inflicted skin diseases: a retrospective analysis of 57 patients with dermatitis artefacta seen in a dermatology department. *Acta Derm Venereol*. 2005;85:512–515.
221. Lavery MJ, Stull C, McCaw I, et al. Dermatitis artefacta. *Clin Dermatol*. 2018;36:719–722.
222. Kingston ME, Mackey D. Skin clues in the diagnosis of life-threatening infections. *Rev Infect Dis*. 1986;8:1–11.
223. Bourelly PE, Grossman ME. Subcutaneous nodule as a manifestation of *Pseudomonas* sepsis in an immunocompromised host. *Clin Infect Dis*. 1998;26:188–189.
224. Huminer D, Siegman-Igra Y, Morduchowicz G, et al. Ecthyma gangrenosum without bacteremia: report of six cases and review of the literature. *Arch Intern Med*. 1987;147:299–301.
225. Reich HL, Williams Fadeyi D, Naik NS, et al. Nonpseudomonal ecthyma gangrenosum. *J Am Acad Dermatol*. 2004;50(suppl):S114–S117.
226. Benoit FL. Chronic meningococcemia. *Am J Med*. 1963;35:103–112.
227. Lefèvre B, Poinsignon Y, Piau C, et al. Chronic meningococcemia: a report of 26 cases and literature review. *Infection*. 2019;47:285–288.
228. Dupin N, Lecuyer H, Carlotti A, et al. Chronic meningococcemia cutaneous lesions involve meningococcal perivascular invasion through the remodeling of endothelial barriers. *Clin Infect Dis*. 2012;54:1162–1165.
229. O' Brien JP, Goldenberg DL, Rice PA. Disseminated gonococcal infection: a prospective analysis of 49 patients and a review of pathophysiology and immune mechanisms. *Medicine (Baltimore)*. 1983;62:395–406.
230. Rice PA. Gonococcal arthritis (disseminated gonococcal infection). *Infect Dis Clin North Am*. 2005;19:853–861.
231. Rompalo AM, Hook EW 3rd, Roberts PL, et al. The acute arthritis-dermatitis syndrome: the changing importance of *Neisseria gonorrhoeae* and *Neisseria* meningitidis. *Arch Intern Med*. 1987;147:281–283.
232. Crew PE, Abara WE, McCulley L, et al. Disseminated gonococcal infections in patients receiving eculizumab: a case series. *Clin Infect Dis*. 2018;[Epub ahead of print].
233. Chartrand SA, Harrison CJ. Buccal cellulitis reevaluated. *Am J Dis Child*. 1986;140:891–893.
234. Drapkin MS, Wilson ME, Shrager SM, et al. Bacteremic *Haemophilus influenzae* type B cellulitis in the adult. *Am J Med*. 1977;63:449–452.
235. Burman WJ, Cohn DL, Reves RR, et al. Multifocal cellulitis and monoarticular arthritis as manifestations of *Helicobacter cinaedi* bacteremia. *Clin Infect Dis*. 1995;20:564–570.
236. Shimizu S, Inokuma D, Watanabe M, et al. Cutaneous manifestations of *Helicobacter cinaedi* infection. *Acta Derm Venereol*. 2013;93:165–167.
237. Marrie TJ. Osler's nodes and Janeway lesions. *Am J Med*. 2008;121:105–106.
238. Cardullo AC, Silvers DN, Grossman ME. Janeway lesions and Osler's nodes: a review of histopathologic findings. *J Am Acad Dermatol*. 1990;22:1088–1090.
239. Røder BL, Wandall DA, Frimodt-Moller N, et al. Clinical features of *Staphylococcus aureus* endocarditis: a 10-year experience in Denmark. *Arch Intern Med*. 1999;159:462–469.
240. Kimyai-Asadi A, Usman A, Milani F. Cutaneous manifestations of marantic endocarditis. *Int J Dermatol*. 2000;39:290–292.
241. Li Y, Muench A, McGregor DH, et al. Cerebral, myocardial and cutaneous ischemic necrosis associated with calcific emboli from aortic and mitral valve calcification in a patient with end-stage renal disease. *Clin Nephrol*. 2002;57:468–473.
242. Bae GY, Lee HW, Chang SE, et al. Clinicopathologic review of 19 patients with systemic candidiasis with skin lesions. *Int J Dermatol*. 2005;44:550–555.
243. Jarowski CI, Fialk MA, Murray HW, et al. Fever, rash, and muscle tenderness: a distinctive clinical presentation of disseminated candidiasis. *Arch Intern Med*. 1978;138:544–546.
244. Farag SS, Firkin FC, Andrew JH, et al. Fatal disseminated *Scedosporium inflatum* infection in a neutropenic immunocompromised patient. *J Infect*. 1992;25:201–204.
245. Ajmal S, Keating M, Wilhelm M. Multifocal soft tissue cryptococcosis in a renal transplant recipient: the importance of suspecting atypical pathogens in the immunocompromised host. *Exp Clin Transplant*. 2018;[Epub ahead of print].
246. Stone HH, Martin JJ Jr. Synergistic necrotizing cellulitis. *Ann Surg*. 1972;175:702–711.
247. George WL. Other infections of skin, soft tissue, and muscle. In: Finegold SM, George WL, eds. *Anaerobic Infections in Humans*. New York: Academic Press; 1989:492–504.
248. Stevens DL, Bryant AE. Necrotizing soft-tissue infections. *N Engl J Med*. 2017;377:2253–2265.
249. Moses AE, Hardan I, Simhon A, et al. *Clostridium septicum* bacteremia and diffuse spreading cellulitis of the head and neck in a leukemic patient. *Rev Infect Dis*. 1991;15:525–527.
250. MacLennan JD. The histotoxic clostridial infections of man. *Bacteriol Rev*. 1962;26:177–276.
251. Bryant P, Carapetis J, Matussek J, et al. Recurrent crepitant cellulitis caused by *Clostridium perfringens*. *Pediatr Infect Dis J*. 2002;21:1173–1174.
252. Bessman AN, Wagner W. Nonclostridial gas gangrene. *JAMA*. 1975;233:958–963.
253. Lancerotto L, Tocco I, Salmaso R, et al. Necrotizing fasciitis: classification, diagnosis, and management. *J Trauma Acute Care Surg*. 2012;72:560–566.

254. Sarani B, Strong M, Pascual J, et al. Necrotizing fasciitis: current concepts and review of the literature. *J Am Coll Surg*. 2009;208:279–288.
255. Rahim GR, Gupta N, Maheshwari P, et al. Monomicrobial *Klebsiella pneumoniae* necrotizing fasciitis: an emerging life-threatening entity. *Clin Microbiol Infect*. 2019;25: 316–323.
256. Kuehl R, Tschudin-Sutter S, Siegemund M, et al. High mortality of non-Fournier necrotizing fasciitis with Enterobacteriales: time to rethink classification? *Clin Infect Dis*. 2018;[Epub ahead of print].
257. Morgan MS. Diagnosis and management of necrotising fasciitis: a multiparametric approach. *J Hosp Infect*. 2010;75:249–257.
258. Aronoff DM, Bloch KC. Assessing the relationship between the use of nonsteroidal anti-inflammatory drugs and necrotizing fasciitis caused by group A streptococcus. *Medicine (Baltimore)*. 2003;82:225–235.
259. Bryant AE, Bayer CR, Aldape MJ, et al. The roles of injury and nonsteroidal anti-inflammatory drugs in the development and outcomes of severe group A streptococcal soft tissue infections. *Curr Opin Infect Dis*. 2015;28:231–239.
260. Stevens DL, Tanner MH, Winship J, et al. Severe group A streptococcal infections associated with a toxic shock–like syndrome and scarlet fever toxin A. *N Engl J Med*. 1989;321:1–7.
261. Wilson GJ, Talkington DF, Guber W, et al. Group A streptococcal necrotizing fasciitis following varicella in children: case reports and review. *Clin Infect Dis*. 1995;20:1333–1338.
262. Johansson L, Thulin P, Low DE, et al. Getting under the skin: the immunopathogenesis of *Streptococcus pyogenes* deep tissue infections. *Clin Infect Dis*. 2010;51:58–65.
263. Vlaminckx BJ, Schuren FH, Montijn RC, et al. Determination of the relationship between group A streptococcal genome content, M type, and toxic shock syndrome by a mixed genome microarray. *Infect Immun*. 2007;75:2603–2611.
264. Kadri SS, Swihart BJ, Bonne SL, et al. Impact of intravenous immunoglobulin on survival in necrotizing fasciitis with vasopressor-dependent shock: a propensity score-matched analysis from 130 US hospitals. *Clin Infect Dis*. 2017;64:877–885.
265. Llewelyn M. Human leukocyte antigen class II haplotypes that protect against or predispose to streptococcal toxic shock. *Clin Infect Dis*. 2005;41(suppl 7):S445–S448.
266. Casali RE, Tucker WE, Petrino RA, et al. Postoperative necrotizing fasciitis of the abdominal wall. *Am J Surg*. 1980;140:787–790.
267. Underwood TJ, Southgate J, Talbot R, et al. Perforated diverticulitis presenting as necrotising fasciitis of the leg. *World J Emerg Surg*. 2008;3:10.
268. Chen JL, Fullerton KE, Flynn NM. Necrotizing fasciitis associated with injection drug use. *Clin Infect Dis*. 2001;33:6–15.
269. Kimura AC, Higa JI, Levin RM, et al. Outbreak of necrotizing fasciitis due to *Clostridium sordellii* among black-tar heroin users. *Clin Infect Dis*. 2004;38:e87–e91.
270. Fraser N, Davies BW, Cusack J. Neonatal omphalitis: a review of its serious complications. *Acta Paediatr*. 2006;95:519–522.
271. Goh T, Goh LG, Ang CH, et al. Early diagnosis of necrotizing fasciitis. *Br J Surg*. 2014;101:e119–e125.
272. Anaya DA, Dellinger EP. Necrotizing soft-tissue infection: diagnosis and management. *Clin Infect Dis*. 2007;44:705–710.
273. Eke N. Fournier's gangrene: a review of 1726 cases. *Br J Surg*. 2000;87:718–728.
274. Corcoran AT, Smaldone MC, Gibbons EP, et al. Validation of the Fournier's gangrene severity index in a large contemporary series. *J Urol*. 2008;180:944–948.
275. Hagedorn JC, Wessells H. A contemporary update on Fournier's gangrene. *Nat Rev Urol*. 2017;14:205–214.
276. Iorianni P, Oliver GC. Synergistic soft tissue infections of the perineum. *Dis Colon Rectum*. 1992;35:640–644.
277. Voelzke BB, Hagedorn JC. Presentation and Diagnosis of Fournier Gangrene. *Urology*. 2018;114:8–13.
278. Ioannidis O, Kitsikosta L, Tatsis D, et al. Fournier's gangrene: lessons learned from multimodal and multidisciplinary management of perineal necrotizing fasciitis. *Front Surg*. 2017;4:36.
279. Bjurlin MA, O'Grady T, Kim DY, et al. Causative pathogens, antibiotic sensitivity, resistance patterns, and severity in a contemporary series of Fournier's gangrene. *Urology*. 2013;81:752–758.
280. Chia L, Crum-Cianflone N. Emergence of multi-drug-resistant organisms (MDROs) causing Fournier's gangrene. *Open Forum Infect Dis*. 2017;4(suppl 1):S111.
281. Lazzeri D, Lazzeri S, Figus M, et al. Periorbital necrotising fasciitis. *Br J Ophthalmol*. 2010;94:1577–1585.
282. Rapoport Y, Himelfarb MZ, Zikk D, et al. Cervical necrotizing fasciitis of odontogenic origin. *Oral Surg Oral Med Oral Pathol*. 1991;72:15–18.
283. Weiss A, Nelson P, Movahed R, et al. Necrotizing fasciitis: review of the literature and case report. *J Oral Maxillofac Surg*. 2011;69:2786–2794.
284. Banerjee AR, Murty GE, Moir AA, et al. Cervical necrotizing fasciitis: a distinct clinicopathological entity? *J Laryngol Otol*. 1996;110:81–86.
285. Murphy JJ, Granger R, Blair GK, et al. Necrotizing fasciitis in childhood. *J Pediatr Surg*. 1995;30:1131–1134.
286. Olsen RJ, Burns KM, Chen L, et al. Severe necrotizing fasciitis in a human immunodeficiency virus–positive patient caused by methicillin-resistant *Staphylococcus aureus*. *J Clin Microbiol*. 2008;46:1144–1147.
287. Majumdar R, Crum-Cianflone NF. Necrotizing fasciitis due to *Serratia marcescens:* case report and review of the literature. *Infection*. 2016;44:371–377.
288. Hagiya H, Ojima M, Yoshida T, et al. Necrotizing soft tissue infection caused by *Serratia marcescens:* a case report and literature review. *J Infect Chemother*. 2016;22:335–338.
289. Sanchez IM, Lowenstein S, Johnson KA, et al. Clinical features of neutrophilic dermatosis variants resembling necrotizing fasciitis. *JAMA Dermatol*. 2019;155:79–84.
290. Anaya DA, McMahon K, Nathens AB, et al. Predictors of mortality and limb loss in necrotizing soft tissue infections. *Arch Surg*. 2005;140:151–157.
291. Mills MK, Faraklas I, Davis C, et al. Outcomes from treatment of necrotizing soft-tissue infections: results from the National Surgical Quality Improvement Program database. *Am J Surg*. 2010;200:790–796.
292. Schmid MR, Kossman T, Duewell S. Differentiation of necrotizing fasciitis and cellulitis using MR imaging. *AJR Am J Roentgenol*. 1998;170:615–620.
293. Fayad LM, Carrino JA, Fishman EK. Musculoskeletal infection: role of CT in the emergency department. *Radiographics*. 2007;27:1723–1736.
294. Levenson RB, Singh AK, Novelline RA. Fournier gangrene: role of imaging. *Radiographics*. 2008;28: 519–528.
295. Morrison D, Blaivas M, Lyon M. Emergency diagnosis of Fournier's gangrene with bedside ultrasound. *Am J Emerg Med*. 2005;23:544–547.
296. Chingkoe CM, Jahed A, Loreto MP, et al. Retroperitoneal fasciitis: spectrum of CT findings in the abdomen and pelvis. *Radiographics*. 2015;35:1095–1107.
297. Hayeri MR, Ziai P, Shehata ML, et al. Soft-tissue infections and their imaging mimics: from cellulitis to necrotizing fasciitis. *Radiographics*. 2016;36:1888–1910.
298. Stamenkovic I, Lew PD. Early recognition of potentially fatal necrotizing fasciitis: use of frozen-section biopsy. *N Engl Med*. 1984;310:1689–1693.
299. Koch C, Hecker A, Grau V, et al. Intravenous immunoglobulin in necrotizing fasciitis: a case report and review of recent literature. *Ann Med Surg (Lond)*. 2015;4:260–263.
300. Kaide CG, Khandelwal S. Hyperbaric oxygen: applications in infectious disease. *Emerg Med Clin North Am*. 2008;26:571–595.
301. Devaney B, Frawley G, Frawley L, et al. Necrotising soft tissue infections: the effect of hyperbaric oxygen on mortality. *Anaesth Intensive Care*. 2015;43:685–692.
302. Abrahamian FM, Goldstein EJ. Microbiology of animal bite wound infections. *Clin Microbiol Rev*. 2011;24:231–246.
303. Brook I. Management of human and animal bite wounds: an overview. *Adv Skin Wound Care*. 2005;18:197–203.
304. Bula-Rudas FJ, Olcott JL. Human and animal bites. *Pediatr Rev*. 2018;39:490–500.
305. Chin RL, Martinez R, Garmel G. Gas gangrene from subcutaneous insulin administration. *Am J Emerg Med*. 1993;11:622–625.
306. Delie A, Vlummens P, Creytens D, et al. Cutaneous mucormycosis as result of insulin administration in an AML patient: case report and review of the literature. *Acta Clin Belg*. 2017;72:352–356.
307. Ebright JR, Pieper B. Skin and soft tissue infections in injection drug users. *Infect Dis Clin North Am*. 2002;16:697–712.
308. Biderman P, Hiatt JR. Management of soft-tissue infections of the upper extremity in parenteral drug abusers. *Am J Surg*. 1987;154:526–528.
309. Aduan RP, Fauci AS, Dale DC, et al. Factitious fever and self-induced infection: a report of 32 cases and review of the literature. *Ann Intern Med*. 1979;90:230–242.
310. Reich P, Gottfried LA. Factitious disorders in a teaching hospital. *Ann Intern Med*. 1983;99:240–247.
311. Thomsen IP, Smith MA, Holland SM, et al. A Comprehensive Approach to the Management of Children and Adults with Chronic Granulomatous Disease. *J Allergy Clin Immunol Pract*. 2016;4:1082–1088.
312. Sillevis Smitt JH, Kuijpers TW. Cutaneous manifestations of primary immunodeficiency. *Curr Opin Pediatr*. 2013;25:492–497.
312a. Grimbacher B, Holland SM, Puck JM. Hyper-IgE syndromes. *Immunol Rev*. 2005;203:244–250.
313. Shahin GS, Lerner SA. Rare presentation of *Streptococcus pneumoniae* pneumonia with bacteremia and multiple subcutaneous abscesses. *Eur J Clin Microbiol Infect Dis*. 2002;21:611–612.
314. Patel VJ, Gardner E, Burton CS. *Vibrio vulnificus* septicemia and leg ulcer. *J Am Acad Dermatol*. 2002;46(suppl):S144–S145.
315. Curley RK, Hayward T, Holden CA. Cutaneous abscesses due to systemic nocardiosis. *Clin Exp Dermatol*. 1990;15:459–461.
316. Olson JM, Nguyen VQ, Yoo J, et al. Cutaneous manifestations of *Corynebacterium jeikeium* sepsis. *Int J Dermatol*. 2009;48:886–888.

94 Myositis and Myonecrosis

Mark S. Pasternack

SHORT VIEW SUMMARY

Definition

- Myositis is an inflammatory and generally necrotizing process primarily due to hematogenous seeding of muscle with subsequent bacterial invasion. Direct inoculation of muscle as the result of penetrating trauma is also an important mechanism of infection (associated with clostridial myonecrosis). More generalized muscle inflammation may also accompany a variety of acute and chronic viral and parasitic disorders.

Epidemiology

- Pyomyositis occurs across the age spectrum in temperate regions and may occur in previously healthy as well as immunocompromised individuals; in warm climates infections in children predominate (i.e., tropical pyomyositis). Clostridial myonecrosis most commonly complicates penetrating trauma (e.g., vehicular accidents, war, natural disasters), especially in resource-limited settings.

Microbiology

- *Staphylococcus aureus* is the classic cause of pyomyositis, but similar illnesses have been associated with a wide variety of bacterial pathogens, particularly in compromised hosts. *Clostridium perfringens* myonecrosis complicates penetrating trauma, but nontraumatic clostridial myonecrosis may develop after hematogenous dissemination of more aerotolerant species (e.g., *Clostridium septicum, Clostridium sordellii*). Group A streptococci can also cause severe myonecrotic infection, which is a true medical emergency. Acute generalized muscle inflammation occurs after influenza and dengue virus infections, but a wide variety of viral pathogens have sporadically led to significant muscle injury and even severe rhabdomyolysis.

Diagnosis

- Consideration of these uncommon processes is the first step toward the proper diagnosis because the focal progressive pain of pyomyositis mimics a variety of infectious and noninfectious disorders. Blood cultures and (percutaneous) drainage based on the findings of cross-sectional imaging, with subsequent microbiologic characterization, confirm the diagnosis and guide therapy. Pyomyositis may accompany toxic shock, and investigation of a focal process responsible for fulminant systemic illness is essential. Gas production in muscle and soft tissue in the setting of a rapidly progressive illness occurs in clostridial myonecrosis and related infections; this is a surgical emergency and exploration for débridement of nonviable tissue and appropriate cultures is critical.

Therapy

- Ideally, after expedited imaging and drainage, empirical broad-spectrum antibacterial therapy effective against *Staphylococcus aureus,* including methicillin-resistant *S. aureus*, and gram-negative bacilli and anaerobes should be administered. The findings of associated toxic shock mandate the addition of a protein synthesis inhibitor (e.g., clindamycin). There is a lack of evidence supporting the use of intravenous immunoglobulin therapy in this setting. Narrow-spectrum therapy is appropriate after identification and sensitivity testing of the isolated pathogen. Patients presenting with the clinical findings of gas gangrene (clostridial myonecrosis) require immediate high-dose penicillin and clindamycin and urgent surgical exploration.

Prevention

- Because most episodes of pyomyositis develop after transient bacteremia, prevention is not practical. Prompt débridement of devitalized tissue after penetrating injury is highly effective at preventing clostridial myonecrosis.

Infection of skeletal muscle (infectious myositis) is uncommon. When it occurs, a wide range of organisms may be responsible: bacteria, mycobacteria, fungi, viruses, and parasitic agents.[1] Bacteria invade muscle either from contiguous sites of infection (e.g., skin and subcutaneous abscesses, penetrating wounds, decubitus ulcers, osteomyelitis) or by hematogenous spread from a distant focus. It is helpful to categorize infectious myositis on the basis of clinical manifestations. These may be very distinctive, as in clostridial gas gangrene, and suggest the specific etiologic agent, or they may be very nonspecific, as in the myalgias of viral infections and infective endocarditis (Table 94.1). In certain instances (e.g., psoas abscess) it is the anatomic location rather than the morphologic characteristics of the lesion or the nature of the infecting agent that distinguishes the particular type of muscle infection.

PYOMYOSITIS

Pyomyositis is an acute bacterial infection of skeletal muscle that is most commonly caused by *Staphylococcus aureus.* After seeding of muscle and initial phlegmon development, pus accumulates within muscles; the muscle infection is not usually due to primary infection of adjacent skin, soft tissue, or bone. Clinically, pyomyositis is characterized by fever, localized muscle pain and stiffness, swelling, and tenderness.

Pathogenesis and Pathologic Characteristics

Bacterial infections of muscle usually occur after a penetrating wound, prolonged vascular insufficiency in an extremity, or a contiguous infection. Bacteremic spread of infection to skeletal muscle is extremely uncommon. Among fatal cases of staphylococcal septicemia, abscesses in skeletal muscle are found in less than 1%.[2] Pyomyositis (primary muscle abscess) is a bacterial infection of muscle that occurs in the absence of a predisposing site of infection. *S. aureus* is the most common cause.[3,4] Blood cultures are positive in 5% to 35% of the cases in most series at the time of presentation; metastatic infections in tissue other than muscle are rare, although multifocal pyomyositis,[5,6] distant hematogenous osteomyelitis,[7] and the development of venous thrombosis and septic pulmonary emboli have been reported.[8] In individual patients with multifocal infections or associated endocarditis, it may be challenging to clarify whether sustained bacteremia was the primary process or the result of progressive pyomyositis.[9,10]

Most cases of pyomyositis occur in the tropics, hence the term *tropical pyomyositis.* Historically, it accounted for 1% to 4% of hospital admissions in some tropical areas,[11] although recently in northern India pyomyositis accounted for only 0.03% of admissions.[12] In more temperate areas, pyomyositis is very uncommon, with approximately 330 reported cases

TABLE 94.1 Classification of Infectious Myositis

TYPE OF PROCESS	CLINICAL PATTERN	SPECIFIC CAUSES
Pyogenic and predominantly localized (spreading by contiguity)	Pyomyositis	*Staphylococcus aureus* Group A streptococci (occasionally) Other gram-positive cocci (rarely) Group B, C, or G streptococci *Streptococcus pneumoniae* Gram-negative bacilli (rarely) Anaerobic bacteria (rarely) *Fusobacterium necrophorum* Clostridia Mycobacteria (rarely) *Mycobacterium tuberculosis* *Mycobacterium avium-intracellulare* Fungi (rarely) *Cryptococcus neoformans*
	Gas gangrene	*Clostridium perfringens;* on occasion other histotoxic clostridial species
	Nonclostridial (crepitant) myositis	
	Anaerobic streptococcal gangrene	*Peptostreptococcus* (plus group A streptococci or *S. aureus*)
	Group A streptococcal necrotizing myositis	Group A streptococci
	Synergistic nonclostridial anaerobic myonecrosis	Mixed infections: *Bacteroides* and other anaerobic non–spore-forming gram-negative bacilli; *Peptostreptococcus* and various streptococci; *Escherichia coli; Klebsiella; Enterobacter*
	Infected vascular gangrene	Same as for synergistic nonclostridial anaerobic myonecrosis
	Aeromonas hydrophila myonecrosis	*A. hydrophila*
	Psoas abscess	Gram-negative bacilli; *S. aureus;* mixed infections; *M. tuberculosis*
Nonpyogenic and predominantly generalized	Myalgias	Viral infections (e.g., influenza, dengue); infective endocarditis; bacteremias (e.g., meningococcemia); rickettsioses (e.g., Rocky Mountain spotted fever); toxoplasmosis
	Pleurodynia	Coxsackievirus B
	Myalgias with eosinophilia	
	Trichinosis	*Trichinella spiralis, Trichinella pseudospiralis*
	Cysticercosis (also subcutaneous nodules)	*Taenia solium*
	Muscle degeneration and destruction associated with infections elsewhere	
	Acute rhabdomyolysis	Influenza viruses, dengue virus, echoviruses, coxsackieviruses, Epstein-Barr viruses, *Legionella,* and others (see text)

in the United States between 1981 and 2002[4] and a reported incidence of 0.5 per 100,000 annually in Australia early in this century.[9] More recently the annual incidence in selected regions in Australia has risen to as high as 13.5 per 100,000.[12a] Pyomyositis occurs at all ages, in the tropics more frequently among children,[13] but in North America more often in adults and the elderly.[4,14] No convincing evidence relates pyomyositis causally to predisposing circumstances peculiar to the tropics (e.g., malaria, filariasis, arbovirus infection). However, an association between *Toxocara canis* infection (visceral larva migrans) and staphylococcal pyomyositis has been proposed.[15] Migration of the guinea worm *Dracunculus medinensis* in the deep connective tissues of the lower extremities may be complicated by staphylococcal abscesses, but these are located between muscle groups and are not the intramuscular abscesses typical of pyomyositis. Approximately 40% of cases in temperate climates lack any relevant underlying disease, but the remainder have possible predisposing risk factors, such as intravenous (IV) drug abuse and systemic conditions, including human immunodeficiency virus (HIV) infection, diabetes mellitus, alcoholic liver disease, corticosteroid therapy, hematologic malignancies (e.g., leukemia, lymphoma, or multiple myeloma), other hematologic processes (e.g., Felty syndrome, myelodysplasia, sickle cell disease, cyclic neutropenia, chronic granulomatous disease) and/or their cytotoxic therapies, and rheumatologic diseases (particularly rheumatoid arthritis and systemic lupus erythematosus).[4,14] The postpartum,[16] postabortion,[17] and postoperative states, as well as deep acupuncture,[18] are rare predisposing risk factors for the development of pyomyositis.

Pyomyositis has been reported repeatedly in patients with HIV infection, with or without acquired immunodeficiency syndrome (AIDS) (including one neonate); in the majority of these patients it was caused by *S. aureus.*[4,19] The predisposition to pyomyositis in AIDS patients probably relates to granulocyte dysfunction,[20] progressive cell-mediated immunodeficiency,[21] and possible muscle injury (e.g., HIV myopathy, zidovudine-associated mitochondrial myopathy, myositis from parasitic disease, *Mycobacterium avium* complex infection). Although *S. aureus* is the etiologic agent in the majority of HIV-associated cases, *Salmonella* accounts for as many as 10% and streptococci for 5% of pyomyositis episodes in this population[4,19]; pneumococci, enterococci, and granulomatous infections due to *Mycobacterium tuberculosis* and *Sporothrix schenckii* have also been reported. Pyomyositis has been reported in growing numbers of IV drug abusers (with or without HIV infection) caused primarily by *S. aureus* but also by streptococci, gram-negative bacilli, or multiple organisms (including anaerobes).[22] Pyomyositis is a rare complication of bacterial endocarditis and has been reported in an IV drug abuser who had left-sided *S. aureus* infection[9,23] and in a patient with subacute endocarditis due to *S. haemolyticus.*[10]

The presumed pathogenesis of (primary) pyomyositis is thought to reflect initial bacteremia, commonly asymptomatic and transient. Because muscle trauma (locus minoris resistentiae) is necessary to produce pyomyositis in experimental animals after IV injection of *S. aureus,*[24] a role for local mechanical injury has been hypothesized. Secondary pyomyositis reflects spread of infection from a contiguous source, typically a site of hematogenous osteomyelitis. The frequency of pyomyositis complicating staphylococcal osteomyelitis may be increased in community-acquired methicillin-resistant *S. aureus* (MRSA) strains expressing Panton-Valentine leukocidin[25] and, in general, molecular features of distinct *S. aureus* clones correlate with superficial or invasive clinical syndromes.[26]

Clinical Manifestations

In 20% to 50% of cases there has been recent blunt trauma to or vigorous exercise of the involved area or a local primary dermatologic process.[4,9] The clinical picture often involves three stages. In the first, or invasive, stage, the onset is subacute with variable fever, local swelling with or without erythema, mild pain, and minimal tenderness. Noninfectious processes such as torticollis or muscle sprain are often considered, particularly if fever is not prominent.[27] The area is indurated or has a

wooden consistency. This stage is often overlooked. Because the initial swelling is firm and pain is not striking, and/or involves deep muscles not easily assessed at the bedside, attention is directed away from an infectious cause. Aspiration, if attempted, yields no pus. The second, or suppurative, stage occurs 10 to 21 or more days later, and this is the time when most patients are diagnosed. The patient is febrile, and distinct muscle tenderness and swelling (conforming to the involved muscle) are present. The overlying skin is intact and warm, and erythema is commonly absent. At this point pus can be aspirated from the involved muscle. In the third stage, systemic manifestations of sepsis and local findings of erythema, exquisite tenderness, and fluctuance are striking. If untreated the infection can progress to metastatic abscesses, shock, renal failure, and death[28]; the overall mortality rate is approximately 5%[4] and is largely associated with the presence of severe sepsis and septic shock.[4] The progression of pyomyositis from the initial invasive stage, associated with muscle inflammation and swelling, to the suppurative stage, with focal abscess formation, was documented by serial imaging in a patient whose infection was initially managed with antibiotic therapy.[29]

On occasion, the onset is acute rather than subacute, with malaise, chills, and high fever. Rarely, the clinical picture is combined with that of toxic shock syndrome.[30,31] This is a particular risk of myositis caused by group A β-hemolytic streptococci (see later discussion). Because the muscle abscesses are contained by the overlying fascia, local erythema and warmth may be minimal and the severity of the process not appreciated until the infection extends to the subcutaneous tissues some days to weeks later. Regional lymphadenitis is not a feature. Usually only a single muscle group is involved, but multiple muscle abscesses may be present at presentation[32] and so prominent as to mimic critical illness myopathy[6] or develop after contiguous spread (e.g., from the psoas to the thigh adductors[33]). The most frequent sites of involvement are the large muscles of the lower extremities (e.g., quadriceps femoris, gluteus group) and the trunk muscles, but a variety of other muscles can be involved (Fig. 94.1) including the smaller hip rotators (obturator internus and externus, piriformis), cervical paraspinal muscles,[34] sternocleidomastoids, and even ocular muscles.[35] Involvement of the abdominal muscles is uncommon[7] but noteworthy because it may mimic an acute abdomen.[36] Even in fatal cases, the diagnosis may be overlooked and involvement of superficial muscles may be missed at autopsy.[28]

Leukocytosis is prominent; eosinophilia is common in patients with tropical pyomyositis (even in the presence of a prominent granulocytosis) and may simply reflect concomitant parasitic infestation. Serum muscle enzyme levels may be elevated, particularly with severe streptococcal disease, but they frequently are normal despite gross muscle destruction. However, marked rhabdomyolysis with myoglobinuria and acute renal failure, more commonly seen in viral myositis, was reported in a patient with pyomyositis.[37]

Etiologic Agents

S. aureus is responsible for 95% of tropical pyomyositis cases, whereas in temperate areas *S. aureus* is the cause of 66% to 70% of cases.[4,14] Group A streptococci account for 1% to 5% of the cases. Other gram-positive organisms uncommonly implicated in pyomyositis include various streptococci (groups B, C, and G), *Streptococcus pneumoniae,*[38] *Enterococcus faecalis,*[39] and *Streptococcus anginosus.*[40] Myositis due to viridans streptococci complicating the viridans streptococcal sepsis syndrome in acute myelogenous leukemia has been reported.[41] Pyomyositis due to a dual infection by the coagulase-negative staphylococci *Staphylococcus capitus* and *Staphylococcus saccharolyticus* was reported in a diabetic host.[34] Other very rare causes include Enterobacteriaceae[1] (*Escherichia coli* [particularly in neutropenic patients with hematologic malignancy[42]], *Klebsiella oxytoca, Klebsiella pneumoniae, Serratia marcescens, Morganella morganii, Citrobacter freundii, Enterobacter* spp., *Salmonella* spp.[43]), *Yersinia enterocolitica, Francisella novicida,*[44] *Neisseria gonorrhoeae, Haemophilus influenzae, Pseudomonas aeruginosa, Burkholderia cenocepacia,*[45] and *Aeromonas hydrophila.* Anaerobes (*Fusobacterium nucleatum, F. necrophorum,*[46] *Veillonella* spp., oral anaerobic streptococci,[47] *Capnocytophaga sputigena,*[48] actinomycetes, and *Clostridium septicum*) have been the cause in several cases. Pyomyositis may be caused by mixed pathogens, especially in patients with diabetes mellitus in whom, in addition to *S. aureus,* gram-negative or anaerobic pathogens, or both, were recovered in approximately 35% of episodes,[49] and dual infection by coagulase negative staphylococci was observed.[34] In the past *Burkholderia mallei* and *Burkholderia pseudomallei* have very rarely caused muscle abscesses in the septicemic or chronic suppurative forms of glanders and melioidosis, respectively. *Aspergillus fumigatus* has caused a localized muscle abscess in rare patients with myelodysplasia or AIDS and in patients who have received corticosteroids.

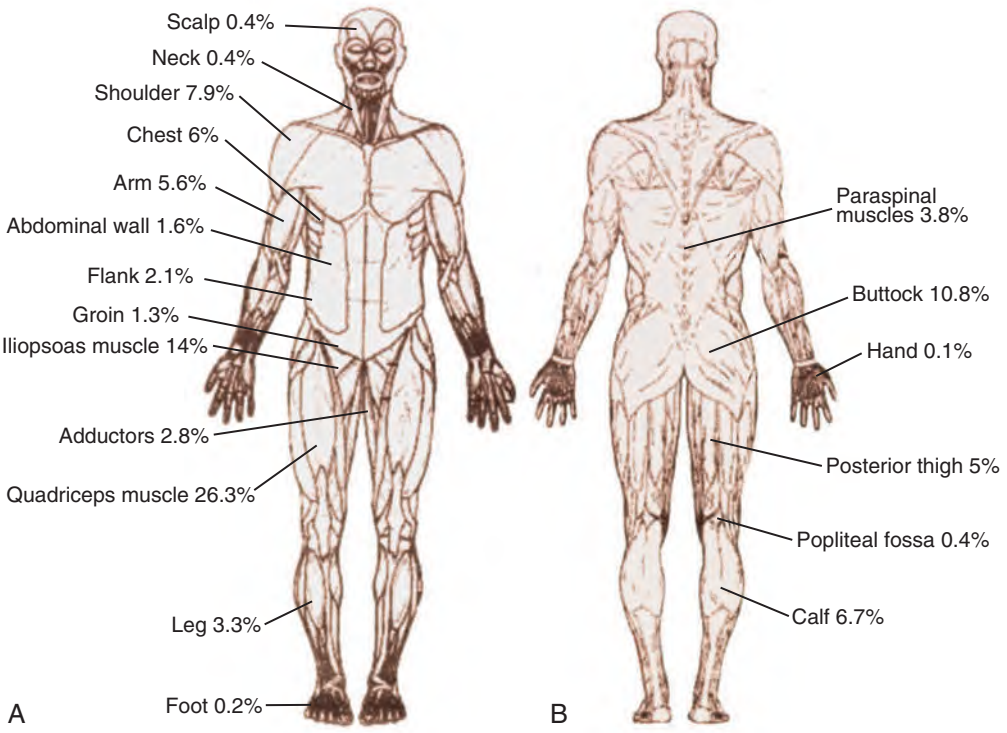

FIG. 94.1 Distribution of sites of pyomyositis. (A) Anterior view. (B) Posterior view. *(Modified from Bickels J, Ben-Sira L, Kessler A, et al. Primary pyomyositis.* J Bone Joint Surg Am. *2002;84:2277–2286.)*

Fusarium spp. has been reported to cause bilateral lower limb pyomyositis in a patient with relapsed acute myelogenous leukemia.[50] Pathogenic yeasts can cause myositis on rare occasions. Pyomyositis due to *Cryptococcus neoformans* was reported in an immunocompromised host,[51] and multifocal *Histoplasma capsulatum* nodular myositis was identified in an HIV-infected patient.[52] Hematogenously disseminated candidiasis in neutropenic patients can manifest as fever and muscle pain. The scattered *Candida* abscesses in the muscle are generally too small to localize by symptoms and physical examination, but myositis in these patients is often accompanied by small, tender, erythematous, hematogenously disseminated skin lesions. Punch biopsy of a skin lesion shows numerous *Candida* organisms in the dermis. Larger candidal lesions may be identified and managed using conventional imaging approaches.[53] Tuberculous pyomyositis is a rare form of extrapulmonary tuberculosis recognized in both competent[54] and immunocompromised[55] hosts and can present with or without features of disseminated disease.[54] Pyomyositis due to *M. avium* complex is occasionally diagnosed in HIV-infected patients, sometimes as part of the immune reconstitution syndrome,[56] and *Mycobacterium haemophilum* pyomyositis was observed in a renal transplant recipient.[57] Extrapulmonary *Pneumocystis jirovecii* infection is relatively uncommon in patients with AIDS, but in one patient it manifested as an intramuscular, localized, painful thigh swelling with typical granulomatous histopathology.[58]

Differential Diagnosis

Early in the course of pyomyositis, other diagnoses may be suspected, particularly in nontropical areas: fever of obscure origin (in the early phase, when localizing findings may be minimal or absent), osteomyelitis, septic arthritis, appendicitis or diverticulitis, muscle strain, contusion or hematoma, muscle rupture, and thrombophlebitis. Iliopsoas myositis has mimicked appendicitis[59]; obturator internus, iliacus, and rarely obturator externus pyomyositises have mimicked septic arthritis of the hip[60]; and pyriformis muscle pyomyositis has simulated an epidural abscess because of severe back and radiating (sciatic) leg pain.[61] Rarely, pyomyositis of the erector spinae[62] or piriformis[63] can extend to the intraspinal canal, leading to a true spinal epidural abscess. Pyomyositis involving deep pelvic muscles may be difficult to diagnose in patients with active joint disease, such as rheumatoid arthritis, in whom symptoms may readily be attributed to the primary disease. Muscle infarction is an uncommon condition that occurs most frequently in the quadriceps muscle in patients with poorly controlled diabetes mellitus with nephropathy, neuropathy, and hypertension. It may suggest pyomyositis because of the acute onset of pain and presence of tender local swelling, but, in contrast to pyomyositis, fever is absent.[64,65] In the patient with multiple sites of muscle involvement and eosinophilia (from incidental parasitic infestation), the picture may initially suggest trichinosis. Rupture of the muscle abscess through the fascia into subcutaneous tissues may suggest the diagnosis of cellulitis. The presence of a slowly enlarging, painful mass in an extremity of a patient with only low-grade fever may suggest the diagnosis of sarcoma. Pyomyositis of the pectoral muscle can pose a particular diagnostic problem because it must be distinguished not only from muscle rupture, hematoma, and sarcoma but also from cryptic abscessed subpectoral nodes complicating infection of the ipsilateral thumb or index finger. Streptococcal necrotizing fasciitis, like gangrenous streptococcal myositis, manifests initially as local pain disproportionate to any physical findings. Localized swelling, tenderness, and erythema ensue, but only in advanced stages are the characteristic violaceous skin changes, bullae, and frank skin necrosis seen overlying areas of fascial necrosis. Rapid frozen-section biopsy or surgical exploration may be needed to distinguish among these processes.

Diagnosis

Prompt imaging is essential in the evaluation of patients with focal soft tissue pain and fever because the possible need for surgical exploration must be assessed urgently. Plain radiographs can demonstrate focal soft tissue swelling, the presence of gas in the soft tissues, and any primary skeletal abnormalities (e.g., fracture, osteomyelitis, osteosarcoma). Ultrasonography is readily accessible and can demonstrate muscle enlargement in the initial stage of pyomyositis; it can also show the presence of focal abscess formation in the suppurative stage of disease, revealing hypoechoic areas with internal echoes,[66–68] especially if symptoms are localized in an extremity. Ultrasound assessment of the hip can detect the presence of a joint effusion, but it may be less sensitive in assessing the deep pelvic musculature. Ultrasonography is usually followed by cross-sectional imaging to gain greater anatomic detail and should not delay definitive imaging studies in acutely ill patients.

Magnetic resonance imaging (MRI) has proved invaluable in the assessment of patients with pyomyositis because it identifies focal muscle edema and localizes the presence of focal abscess formation with great precision.[69] MRI can demonstrate enlargement of involved muscles and a slight increase in signal intensity on T1-weighted images in the involved area, with a hypointense central area and a surrounding gadolinium-enhanced rim. It also shows a diffuse increase in signal intensity on T2-weighted images, with a central high-signal-intensity fluid collection surrounded by a low-intensity rim.[70] Computed tomography (CT) is a more readily available cross-sectional modality, often performed during emergency department evaluation that provides less anatomic detail at the inflammatory stage of myositis but is helpful when used to guide percutaneous drainage of an established muscle abscess. CT can reveal low-density areas with loss of muscle planes, central fluid collection, and a surrounding rim of contrast enhancement characteristic of pyomyositis.[66] Enlargement of the involved muscle is usually evident. Superimposed cellulitis may sometimes be evident on CT, namely, skin thickening, stranding of subcutaneous fat with blurring of fat and fascial planes, and subcutaneous venous distention. Radionuclide imaging using indium 111–labeled leukocytes, sometimes performed as dual SPECT (single-photon emission CT)/CT, provides functional and anatomic detail but has not been compared directly with MRI regarding predictive value or cost.[71]

Empirical Therapy

Drainage of all established abscesses is essential, and selection of open or percutaneous drainage via ultrasound or CT guidance depends on the abscess location, size, and complexity and the available expertise. Initial antibiotic therapy should consist of empirical IV vancomycin because of the preponderance of *S. aureus* isolates from these abscesses and the frequent and increasing incidence of MRSA. In compromised hosts or patients with severe disease, empirical high-dose broad-spectrum therapy effective against gram-negative pathogens and anaerobes should be added initially (e.g., β-lactam/β-lactam inhibitor combination such as piperacillin-tazobactam or a carbapenem such as meropenem). Early modification of initial antimicrobial therapy is based on interpretation of a Gram stain of pus and subsequent cultures and susceptibility testing. If a group A *Streptococcus* is isolated, treatment should be changed to high-dose penicillin G and clindamycin (see later discussion). Continued fever after surgical or percutaneous needle drainage of a muscle abscess while the patient is receiving appropriate antimicrobial therapy suggests the presence of other undrained suppurative foci; relapsing or recurrent pyomyositis is frequent among patients with advanced HIV infection.[4] Pyomyositis may be complicated by a compartment syndrome, particularly if it occurs in the forearm[72] or anterior tibial compartments,[73] and may require surgical drainage, fasciotomies, and débridement beyond simple percutaneous drainage.

The prognosis after definitive treatment of pyomyositis is excellent, unless staphylococcal or streptococcal infection is complicated by the presence of toxic shock syndrome.[30,31] The multiorgan failure associated with established toxic shock carries a disturbingly high mortality rate. In the absence of toxic shock, definitive drainage accompanied by prolonged effective antibiotic therapy usually leads to complete resolution of infection with little or no long-term morbidity, even in immunocompromised individuals. Delays in diagnosis and definitive drainage (when drainage is necessary) have led to muscle fibrosis, with the need for widespread excision, and subsequent functional disability.

GROUP A STREPTOCOCCAL NECROTIZING MYOSITIS

In addition to producing an occasional case of typical pyomyositis with abscess formation, on rare occasions group A streptococci cause a fulminant form of myositis, which is a true medical emergency, referred to as peracute streptococcal pyomyositis, streptococcal necrotizing myositis, streptococcal myonecrosis, or spontaneous streptococcal gangrenous

myositis.[74,75] Both necrotizing myositis and necrotizing fasciitis are frequently associated with group A streptococcal toxic shock syndrome.[75,76] The entire clinical course may occur in 2 to 3 days, with intense pain, boardlike swelling of the affected muscle, and fever. The overlying skin may be uninvolved, or it may become erythematous or violaceous and indurated and contain petechiae and bullae.[75] Most cases involve the extremities although the deep hip musculature and other sites are occasionally observed[77] and appear to develop spontaneously without antecedent pharyngitis or tonsillitis. Bacteremia and toxemia are prominent features and contribute to the very high mortality rate (80%–100%).[75] The rapid spread of infection in a closed compartment of muscles can markedly increase intramuscular pressure, resulting in further necrosis of muscle.[78] However, both processes can be simultaneously present in the same area. The compartment syndrome with group A streptococcal myositis (e.g., a tibial compartment syndrome) may develop in the absence of frank fascial and muscle necrosis with muscle bulging and increased pressure secondary to edema and serosanguineous exudate.[79] Progressive weakness of the compartment muscles, which are swollen and tender, severe pain on movement of the lower leg, and overlying cutaneous hyperesthesia underscore the need for urgent decompressive surgery.

Streptococcal necrotizing fasciitis may resemble streptococcal myositis clinically, although the presence of tense bullae and focal skin necrosis is more suggestive of the former; often both conditions are present.[80,81] MRI may disclose the predominantly involved structure, but urgent surgical exploration, always necessary in the setting of suspected toxic shock associated with focal pain and swelling, should provide a clear answer. Rarely, acute streptococcal myositis with toxic shock syndrome is caused by *Streptococcus dysgalactiae* subsp. *equisimilis,* which may be typed as Lancefield group A, C, or G.[81,82]

Laboratory findings include leukocytosis and an elevated serum creatine phosphokinase level, in marked distinction to nonstreptococcal forms of pyomyositis, in which little, if any, creatine phosphokinase elevation occurs. This medical emergency requires prompt clinical diagnosis with verification at surgery. Distinguishing group A streptococcal necrotizing myositis from streptococcal necrotizing fasciitis and spontaneous clostridial myonecrosis may be difficult clinically, but gas in the tissue suggests spontaneous clostridial myonecrosis. In any case, all of these necrotizing soft tissue infections require prompt surgical exploration. Ultrasonography, CT, or MRI usually reveals muscle swelling and fluid collection in muscle compartments. If prolonged delays are encountered in the pursuit of imaging studies, proceeding directly to surgical exploration with an initial limited surgical approach for diagnostic purposes is justified. Cross-sectional imaging is particularly helpful to address the specific site of muscle involvement in patients with hip pain and a compatible illness to guide optimal surgical exploration. Early aggressive surgical intervention with fasciotomy and débridement of necrotic tissue is indicated; in some instances, amputation is required. If the operative Gram stain suggests streptococcal infection, antibiotic therapy should consist of high doses of penicillin G (3 million units IV every 3 hours or 4 million units every 4 hours or adjusted appropriately for renal insufficiency), along with clindamycin (600 mg IV every 6–8 hours).[83] Clinical experience suggests that clindamycin has greater efficacy against group A streptococci in this life-threatening infection (Eagle effect) because of its greater activity against large bacterial populations in stationary phase growth, its more sustained postantibiotic effect, and its suppression of the production of toxins and other virulence factors through its inhibition of bacterial protein synthesis.[75] Unfortunately, the incidence of clindamycin resistance among group A streptococcal isolates has been rising and is now ≈15% in the United States.[84] Monotherapy with clindamycin should be avoided unless clindamycin susceptibility is confirmed by antibiotic susceptibility testing. The use of intravenous immunoglobulin G (IVIG) as an adjunct in the treatment of streptococcal toxic shock to neutralize streptococcal exotoxins and perhaps to modulate the host immune response has gained popularity based on retrospective studies and one small prospective, randomized trial,[85] but conclusive evidence supporting its use remains limited.[86] A large analysis of patient outcomes after presentation with necrotizing soft tissue infection and shock did not demonstrate a beneficial effect of IVIG therapy with regard to survival or length of hospital stay,[87] and consensus regarding its use remains elusive.[88]

GAS GANGRENE (CLOSTRIDIAL MYONECROSIS)

Gas gangrene is a rapidly progressive life-threatening infection of skeletal muscle caused by clostridia (principally *Clostridium perfringens*). It usually occurs after penetrating muscle injury and contamination (as in a dirty traumatic wound) or rarely postoperatively. Nontraumatic gas gangrene, usually caused by *C. septicum,* is a complication of bacteremia often arising from an occult gastrointestinal mucosal lesion, such as an adenocarcinoma, or as a complication of neutropenic colitis (also see Chapter 246).

Pathogenesis and Pathologic Characteristics

Gas gangrene occurs in settings that have in common muscle injury and contamination with soil or other foreign material containing spores of *C. perfringens* or other histotoxic clostridial species.[89] Classic scenarios include (1) accidental traumatic civilian injuries such as compound fracture; (2) penetrating war wounds[90]; (3) surgical wounds, particularly after bowel or biliary tract surgery[91] or septic abortion; and (4) arterial insufficiency in an extremity.[92] Rare cases of gas gangrene have occurred after parenteral injection of medication, including aqueous epinephrine[93]; subcutaneous insulin administration[94]; parenteral injection of methamphetamine or heroin,[95] and even fluoroscopically guided sacroiliac joint injection.[96] Fulminant gas gangrene has complicated routine venipuncture[92] or platelet infusions[97] in patients with granulocytopenia. *C. perfringens* organisms usually are present in large numbers as normal flora in human feces and therefore can endogenously contaminate skin surfaces. Despite a high frequency (as high as 88%) of clostridial contamination of major traumatic open wounds, the incidence of gas gangrene in this setting is only 1% to 2%,[98] emphasizing the importance of devitalized tissue and the presence of foreign bodies in the pathogenesis of gas gangrene. The minimal dose of *C. perfringens* needed to produce fatal gas gangrene in experimental animals is reduced by a factor of 10^6 if the organism is injected into devitalized muscle contaminated with sterile dirt rather than into normal muscle. The policy of prompt, thorough débridement and of leaving wounds open has decreased the incidence of gas gangrene in wartime injuries; only 22 cases among 139,000 combat casualties in Vietnam were reported.[99]

Gas gangrene may occasionally develop in the absence of an obvious external wound. This form of clostridial myonecrosis is designated spontaneous, nontraumatic gas gangrene. Its principal cause is *C. septicum,* a relatively aerotolerant species that spreads by the bacteremic route and is more capable of establishing infection without significant antecedent tissue injury than other clostridia. Intestinal tract abnormalities (colon cancer, diverticulitis, bowel infarction, necrotizing enterocolitis, volvulus) are the major predisposing conditions.[100] Colon cancer, often cryptic, is the most common of these, occurring in as many as 88% of patients with *C. septicum* bacteremia. Other predisposing disorders include leukemia, other causes of neutropenia, and diabetes mellitus. The primary source of infection is probably mucosal ulceration or perforation of the intestinal tract. The spread by the bacteremic route probably accounts for the bilateral multifocal involvement observed in a few patients with spontaneous gas gangrene.[101] However, it may also manifest in the buttocks or flanks after an intraabdominal catastrophe, with rapid extension of infection along the iliopsoas or other deep muscle groups. The progression of *C. septicum* spontaneous gas gangrene may be even more fulminant than that of traumatic *C. perfringens* gas gangrene; the mortality rate of the former is 67% to 100%, with most patients dying within 24 hours after onset.[100]

The involved muscle undergoes rapid disintegration. Initially it may exhibit only pallor, edema, and loss of elasticity. When examined at surgery, it fails to contract on stimulation and does not bleed from a cut surface. Later it becomes discolored (reddish purple, then greenish purple and gangrenous) and friable. Histologically, the muscle fibers show coagulation necrosis, cavities caused by gas production, and a loss of supporting connective tissue; numerous gram-positive bacilli are present. Few, if any, inflammatory cells are present. Among the more than 16 identified clostridial toxins,[102] evidence suggests that the α- and Θ-toxins of *C. perfringens* are major virulence factors that lead to myonecrosis and apparent lack of inflammation at the site of infection

through cytolysis.[103] Intravascular thrombosis due to the local effects of α-toxin on platelets and granulocytes appears to be responsible for the severe herald pain (which may be ischemic) and extensive myonecrosis.[104] In addition to these local effects, the α-toxin provokes systemic hypotension by directly suppressing myocardial contractility and triggering the release of endogenous inflammatory mediators.[105]

Clinical Manifestations

The usual incubation period between injury and the development of clostridial myonecrosis is 2 to 3 days, but it may be as short as 6 hours. The onset is acute. Pain is the earliest and most important symptom, although on occasion a sense of heaviness may be the only initial symptom. Pain rapidly increases in intensity, beyond what would generally be associated with the preceding injury or surgical procedure, and may become excruciating. The patient soon appears severely ill, pale, and sweaty. Hypotension, tachycardia, shock, and renal failure follow. The patient may be apathetic or may be apprehensive and restless but mentally clear. Delirium, stupor, and unconsciousness may supervene. Low-grade fever is frequently present, often with a temperature below 38.3°C (101°F); hypothermia is a poor prognostic sign and is usually associated with shock. Jaundice may become evident. The process may rapidly progress over a period of hours, with a fatal outcome if not treated aggressively.

Initially, tense edema and local tenderness may be the only local findings. Swollen muscle may herniate through an open wound. A serosanguineous, dirty-appearing discharge containing numerous organisms but few leukocytes escapes from the wound and has a peculiar foul odor. Gas bubbles may be visible in the discharge. Crepitus is usually present, but not prominent; sometimes it is completely obscured by very marked edema. The skin adjacent to the wound is initially swollen and white but rapidly takes on a yellowish or bronze discoloration (Fig. 94.2). Tense blebs containing thin, serosanguineous or dark fluid develop in the overlying skin, and areas of green-black cutaneous necrosis appear. In fulminant cases this progresses visibly over 2 to 4 hours, as indicated by advancing edema and crepitation.

Laboratory Findings

The hematocrit is usually decreased, despite progressive local edema and expected hemoconcentration, because of the lysolecithinase activity of clostridial α-toxin and acute hemolysis. Initial leukocytosis is common. *C. perfringens* bacteremia occurs in about 15% of patients with gas gangrene.[106] Intense bacteremia (with associated intravascular hemolysis) occurs more frequently after uterine infection.[107]

A Gram-stained smear of the wound exudate or an aspirate from a cutaneous bleb reveals many large, gram-positive bacilli with blunt ends but few polymorphonuclear leukocytes (see Chapter 246).[101] In almost all cases spores are not evident. The presence of subterminal spores suggests *C. septicum*. Not infrequently, scattered gram-negative bacilli are also present, particularly in grossly contaminated wounds. The growth of *C. perfringens* in culture can be extraordinarily rapid (generation time as little as 8 minutes), paralleling the rapid advance of the infection in devitalized tissue. Examination of liquid anaerobic cultures for gas production ("stormy fermentation") and subsequent Gram-stain examination as early as 6 hours after inoculation may provide an early presumptive diagnosis of the infecting species. Radiographs and CT scans of the involved areas show extensive and progressive gaseous dissection of muscle and fascial planes.

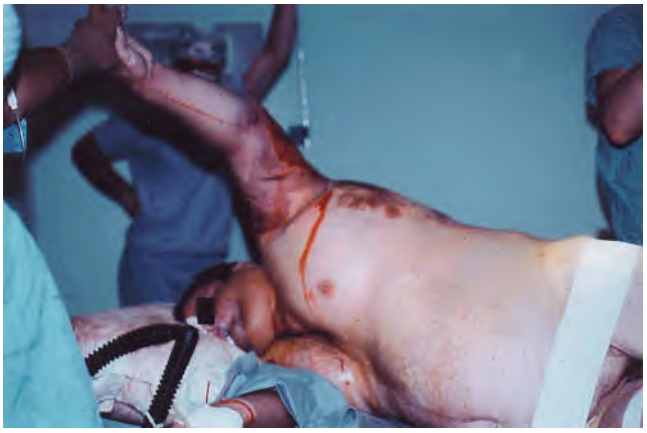

FIG. 94.2 Clostridial gas gangrene of the left upper extremity. There is prominent characteristic bronze discoloration of the skin extending over the shoulder. Crepitus could be palpated beyond the area of discoloration onto the back.

Etiologic Agents

C. perfringens is most commonly isolated from the lesions of gas gangrene (80%–95% of the cases).[90,99] *Clostridium novyi* is involved in 10% to 40% of the cases and *C. septicum* in 5% to 20%. Other clostridial species (e.g., *C. bifermentans, C. histolyticum, C. fallax, C. ramosum,* and *C. sordellii*) have been implicated on rare occasions (e.g., *C. sordellii* with home abortions).[89] In addition to clostridia, other organisms (e.g., *E. coli, Enterobacter* spp., enterococci) are sometimes isolated from the lesions of gas gangrene, reflecting the contaminated character of the initiating trauma or lesion.[106]

Differential Diagnosis

The major differential diagnostic considerations are other gas-forming infections of the soft tissues (clostridial anaerobic cellulitis, nonclostridial crepitant myositis, nonclostridial crepitant cellulitis). Clostridial anaerobic cellulitis (see Chapter 93) is more gradual in onset and progression, and the systemic manifestations of illness are much milder than in gas gangrene. Local pain is relatively mild, and the skin lesions of gas gangrene (bronzing, dark blebs) do not develop. Paradoxically, gas formation is often much more extensive in clostridial cellulitis than in gas gangrene. Clinically, it is often difficult to distinguish between early clostridial cellulitis and myonecrosis. Definitive evaluation requires examination in the operating room for the characteristic changes of myonecrosis described earlier. The clinical picture of nonclostridial crepitant cellulitis is very similar to that of clostridial cellulitis. Although contamination of a surgical or traumatic wound may be the source of infection in both types of cellulitis, nonclostridial crepitant cellulitis frequently develops in the setting of vascular insufficiency or perirectal infection. Bacteria isolated from nonclostridial crepitant cellulitis include facultative species (e.g., *E. coli, Klebsiella*, various streptococci) and anaerobic bacteria (e.g., *Bacteroides, Peptostreptococcus*). Commonly, these are present in mixed culture and can be seen on the Gram-stained smear of a wound aspirate.

Empirical Therapy

Treatment includes emergency surgical exploration, both to define the nature of the process (gas gangrene vs. crepitant cellulitis) by direct muscle examination at the site of infection and to perform appropriate débridement. Prompt and extensive surgery is the principal element in the treatment of gas gangrene. This includes excision of involved muscles (or amputation if necessary) and fasciotomies to decompress and drain the swollen fascial compartments. Antibiotic therapy is an important adjunct to surgical management. Penicillin G, the traditional antibiotic of choice, is administered in a dose of 2 million units IV every 2 hours or 3 million units IV every 3 hours (24 million units/day) (or adjusted for acute renal insufficiency) for an adult. Currently, combined penicillin and clindamycin (600 mg IV every 6–8 hours) is widely used in treatment. The addition of clindamycin is based on results of experimental studies of fulminant clostridial myonecrosis in mice, in which clindamycin, metronidazole, and tetracycline were each more effective than penicillin.[108] In vitro, the addition of penicillin to metronidazole antagonizes the activity of the latter; in contrast, the combination of penicillin with clindamycin provides slightly greater efficacy than clindamycin alone but significantly enhanced efficacy over that of penicillin alone.[109]

An additional antimicrobial agent (e.g., ciprofloxacin, a third- or fourth-generation cephalosporin, or a carbapenem agent) may be used initially if Gram-stained smears of the wound exudate show gram-negative bacilli and the predominant gram-positive bacilli. Patients who are highly penicillin allergic may be treated with clindamycin; plasmid-mediated resistance to tetracycline and erythromycin is now common

among clostridia. Although the majority of *C. perfringens* isolates are susceptible in vitro to cephalosporins, the second-generation agents cefotetan and cefoxitin appear to have more favorable minimal inhibitory concentrations than the third-generation agent ceftriaxone.[110] *C. perfringens* is highly susceptible in vitro to the carbapenems, metronidazole,[110] and linezolid, but experience with the use of these drugs in clostridial myonecrosis is limited.

The role of hyperbaric oxygen therapy is still debated (see Chapter 50).[111,112] Elevated partial pressures of oxygen are thought to reduce the rate of clostridial replication and to suppress toxin expression.[111] The rarity of clostridial myonecrosis and the limited availability of hyperbaric oxygen facilities has made prospective, controlled clinical trials impractical. Its use should never delay immediate surgical débridement if possible. Its most appropriate role at present seems to be in the management of extensive truncal involvement, for which complete surgical excision would be impossible (paraspinal sites) or mutilating. In a murine model of *C. perfringens* myonecrosis initiated with a high inoculum, clindamycin therapy was more effective than hyperbaric oxygen, and the addition of the latter provided no greater efficacy than clindamycin alone.[113] Initial hyperbaric oxygen therapy may decrease the extent of débridement that is necessary under these circumstances. The efficacy of IV-administered polyvalent gas gangrene antitoxin has never been established clinically, and it is no longer available. Comprehensive ancillary therapy in the intensive care unit (ICU) is essential in the management of gas gangrene, including attention to fluid and electrolyte replacement and maintenance of adequate hematocrit levels through transfusion.

NONCLOSTRIDIAL (CREPITANT) MYOSITIS

Nonclostridial (crepitant) myositis includes four relatively distinct entities that differ from gas gangrene in their clinical picture and bacteriologic characteristics: (1) anaerobic streptococcal myonecrosis, (2) synergistic nonclostridial anaerobic myonecrosis, (3) infected vascular gangrene, and (4) *A. hydrophila* myonecrosis.

Anaerobic Streptococcal Myonecrosis

Anaerobic streptococcal myonecrosis is an acute interstitial myositis that clinically resembles subacute clostridial gas gangrene. The initial manifestations are swelling and a copious seropurulent exudate occurring 3 to 4 days after an injury. Pain develops later, unlike the early occurrence of pain in gas gangrene. Tissue gas is present in muscle and fascial planes but is not extensive. The wound has an unpleasant sour odor. The involved muscles are discolored but do react to stimulation. In contrast to gas gangrene, early cutaneous erythema is prominent. If it is not adequately treated, the infection progresses, with the development of toxemia, frank gangrene, and shock.

Numerous streptococci and polymorphonuclear leukocytes are present in the exudate. The infection is usually mixed (anaerobic streptococci with group A streptococci or *S. aureus*). A mixed infection of muscle with both *Finegoldia magna* and *Bacillus subtilis* has been observed on several occasions in the setting of vascular injury. The clinical picture, along with the appearance of the Gram-stained smear, initially might suggest the diagnosis of clostridial myonecrosis.[114] Treatment involves the use of large doses of penicillin and initial antistaphylococcal therapy, such as vancomycin, if indicated by initial Gram stain along with surgical débridement.

Synergistic Nonclostridial Anaerobic Myonecrosis

Synergistic nonclostridial anaerobic myonecrosis, a severe infection seen particularly in patients with diabetes mellitus and those with neutropenia, is also known as synergistic necrotizing cellulitis (see Chapter 93). It involves skin, subcutaneous tissue, fascia, and muscle. The most extensive involvement is in the subcutaneous tissues and fascia; changes in overlying skin and underlying muscle are usually secondary. Although a mixture of anaerobic and facultative organisms is commonly recovered at surgical exploration, on rare occasions crepitant myonecrosis may be caused by *K. pneumoniae,*[115] *Enterobacter cloacae,*[116] or *Bacillus cereus*[117] unaccompanied by other organisms (aerobic or anaerobic) in high-risk patients. The clinical course is rapidly progressive, often leading to a fatal outcome despite emergency surgical exploration and débridement of necrotic tissue.

Infected Vascular Gangrene

Infected vascular gangrene is a mixed infection that develops in a group of muscles or in a limb that is devitalized as a result of arterial insufficiency, particularly in patients with diabetes mellitus. *Proteus* spp., *Bacteroides* spp., and anaerobic streptococci are among the bacteria found in such lesions. Gas formation and foul-smelling pus are prominent. The infection does not extend beyond the area of vascular gangrene to involve healthy muscle. *Bacillus cereus* infection has been associated with myonecrosis with slight crepitus after thrombosis of arterial grafts in addition to more aggressive posttraumatic infections.[117]

Aeromonas hydrophila Myonecrosis

Rapidly progressive myonecrosis caused by *A. hydrophila,* a facultatively anaerobic gram-negative bacillus, may occur after penetrating trauma in a freshwater environment or in association with fish or aquatic animals.[118,119] Although *Aeromonas* was associated with pyomyositis and a compartment syndrome in neutropenic patients,[120] spontaneous (nontraumatic) myonecrosis due to *Aeromonas* has not been reported in other settings. In a few instances myonecrosis has been accompanied by gas spreading extensively in soft tissue planes. The rapid onset (24–48 hours) and rapid progression after trauma resemble those of clostridial gas gangrene. The prominence of pain, marked edema, serosanguineous bullae, and toxicity, in addition to the presence of gas in fascial planes, adds to the similarity of these conditions, and elicitation of freshwater exposure supports the diagnosis of *Aeromonas* infection. Bacteremia is frequently present. Treatment consists of extensive surgical débridement and prompt initiation of antimicrobial therapy. Most isolates of *Aeromonas* are susceptible in vitro to gentamicin, tobramycin, carbapenems, and ciprofloxacin.[118] Third- and fourth-generation cephalosporins, trimethoprim-sulfamethoxazole, and aztreonam also appear to be active, although individual strains may express β-lactamases that selectively hydrolyze cephalosporins or carbapenems.

PSOAS ABSCESS

Infection of the psoas muscle takes the form of either an abscess or a phlegmon, similar to the progression seen in primary pyomyositis. Unlike pyomyositis of other sites, psoas infections in temperate regions most commonly develop after the spread of infection from an adjacent structure (secondary psoas abscess)[1]; in tropical areas primary psoas abscesses, which develop by the hematogenous route, dominate, and *S. aureus* is the most common cause in this setting.[1,121,122] In adult women, hematogenous psoas abscesses have been observed as a complication of spontaneous vaginal delivery.[16,123] A psoas abscess usually is confined within the psoas fascia, but, on occasion, because of anatomic relationships, infection extends to the buttock, hip, or upper thigh.[33] A psoas abscess may complicate pyogenic, tuberculous, or fungal vertebral osteomyelitis. Tuberculosis was formerly the principal cause of psoas abscesses; now they most commonly result from direct extension of intraabdominal infections (e.g., diverticulitis, appendicitis, Crohn disease),[121] rupture of a colonic adenocarcinoma,[124] or from vertebral infection.[122] On occasion, a psoas abscess results from extension of a perinephric abscess or from secondary infection of a retroperitoneal hematoma. The organisms involved in the spread of infection from an intestinal site are usually members of the aerobic and anaerobic bowel flora. *S. aureus* is the most common cause of psoas abscess secondary to vertebral osteomyelitis.

The iliacus muscle, applied to the ilium in the iliac fossa, forms a conjoined tendon with the lower portion of the psoas muscle. Osteomyelitis of the ilium or septic arthritis of the sacroiliac joint can penetrate the sheaths of either or both muscles in this location, producing an iliacus or psoas abscess.[125]

Clinical manifestations of a psoas abscess include fever, malaise, lower abdominal or back pain, or pain referred to the hip or knee. Initially a primary orthopedic injury is often suspected. A limp may be evident, and flexion deformity of the hip may develop from reflex spasm, suggesting septic arthritis of the hip. The psoas sign is evident. Often a tender mass can be palpated in the groin.

Radiographs may show a bulge produced by a psoas muscle abscess or the presence of gas within the psoas sheath. Calcification in a psoas abscess strongly suggests tuberculosis. CT is the most rapid and sensitive noninvasive imaging technique to assess the psoas and iliacus muscles,[126] although in the early stages of illness subtle asymmetrical psoas enlargement may be overlooked.[127] Ultrasonography is less reliable for detecting small lesions or a phlegmon. Radionuclide imaging is no longer widely used in this situation. CT may show diffuse enlargement of the psoas (phlegmon), a sharply circumscribed, low-density fluid collection (abscess) within the muscle, or the presence of gas within the muscle (indicative of abscess).[126] MRI of the pelvis can reveal enlarged psoas and iliacus muscles displaying grossly abnormal signal intensities.

Pyogenic psoas abscesses require drainage and initial empirical antibiotic therapy based on knowledge of the origin of the infection. CT is often quite valuable for abscess visualization and catheter drainage,[128] with direct surgical drainage reserved for unsuccessful interventional radiologic attempts and instances of inadequate catheter access. Although culture-negative psoas abscesses can be seen when drainage procedures follow an initial course of empirical antibiotic therapy, sterile pseudopsoas abscesses associated with erosive diskitis due to calcium pyrophosphate deposition have been reported.[129] If the process appears to be a phlegmon, repeat CT during the course of antibiotic therapy can confirm resolution of the anatomic changes and help determine the duration of antibiotic therapy.

OTHER SPECIFIC SITES OF MUSCLE ABSCESSES

Infective myositis or pyomyositis may occasionally occur in less common anatomic areas and mimic other more common infections; deep pelvic muscle infections are relatively more common in children. Iliacus pyomyositis[60] and pyomyositis of the adductor muscles or the obturator internus muscle[130] may mimic septic arthritis of the hip, pyriformis pyomyositis may suggest a spinal epidural abscess[61] or pelvic osteomyelitis,[131] and iliopsoas myositis[59] may mimic appendicitis. On occasion, the primary myositis may actually progress to involve adjacent joints, resulting in adjacent septic arthritis.

MYALGIAS

Myalgias are prominent features of a variety of infections, such as dengue, influenza, and Rocky Mountain spotted fever, and are often associated with mildly to moderately elevated levels of creatine phosphokinase.[132] Histologic changes include the presence of virions and variable patchy myonecrosis, often with a paucity of inflammation.[132,133] Clinically significant muscle weakness is occasionally present, often in association with severe rhabdomyolysis (see later discussion).[133–136] In addition to the focal myositis syndromes discussed earlier, a variety of pathogens are associated with acute diffuse muscle injury (culminating in rhabdomyolysis) or with chronic diffuse muscle injury, mimicking autoimmune polymyositis (see Table 94.1). The histopathologic similarities observed between autoimmune muscle injury and the polymyositis associated with certain infectious processes and the demonstration of pathogen-specific antigen recognition by infiltrating lymphocytes suggest that infection may trigger an autoimmune attack on myocytes in at least some instances.[137,138]

Influenza

Muscle aches are common early in the course of influenza.[139] On occasion, severe bilateral muscle pains in the lower limbs may develop in the recovery phase of influenza A or B, particularly in young children, which has been termed *acute benign myositis.*[140,141] Although influenza B is less common than influenza A, the rate of influenza B–associated myositis greatly exceeds that of influenza A.[134,135] Muscle tenderness is demonstrable, principally in the gastrocnemius and soleus muscles, and calf swelling may be present. Deep tendon reflexes and muscle strength are normal, but there is considerable difficulty in walking. The leg pains and muscle tenderness subside in less than 1 week. Increases in serum concentrations of aldolase and creatine phosphokinase, sometimes marked, usually peak within 2 weeks of symptom onset.[141] The specimens from the few biopsies performed have shown either nonspecific degenerative changes or muscle necrosis with polymorphonuclear leukocytic infiltration. Whether this myositis is generally caused by direct viral invasion or by some immunologic or other response is unknown. Direct viral replication within skeletal muscle has been demonstrated in fatal cases of influenza A.[142] Life-threatening rhabdomyolysis with extreme increases in creatine phosphokinase and myoglobin-induced acute renal failure are rarely seen after influenza A infection; the prognosis is favorable but may require fasciotomy for extremity compartment syndrome,[143] short-term dialysis,[136,143] or even extracorporeal membrane oxygenation if myocardial dysfunction is present. Isolated influenza myocarditis[144] and perimyocarditis, sometimes quite severe, with resultant cardiogenic shock[145,146] or pericardial tamponade,[147] can occur in the absence of generalized rhabdomyolysis (see Chapter 165).[148] Interestingly, influenza A–triggered Takotsubo ("stress") cardiomyopathy has been observed.[149]

Infective Endocarditis

Prominent myalgias occur in about 15% of patients with infective endocarditis.[150] They may be either diffuse or localized. The pathogenesis is not known, but in one instance muscle biopsy specimens showed a small focus of muscle fiber destruction and leukocytic infiltration consistent with embolization to a small artery. On rare occasions infective endocarditis may lead to frank pyomyositis,[10,23] pain and weakness with a dermatomyositis-like presentation,[151] or rhabdomyolysis.[152]

Toxoplasmosis

The major features of acute acquired disseminated toxoplasmosis are those of meningoencephalitis, myocarditis, pneumonitis, lymphadenitis, rash, and occasionally hepatitis (see Chapter 278). In rare instances, particularly (but not exclusively[153]) in immunocompromised hosts (e.g., HIV infection,[154] chronic immunosuppressive therapy after organ transplantation, CD4 lymphopenia[155]), polymyositis may be a prominent clinical manifestation resembling autoimmune polymyositis. Marked myalgias, muscle weakness and swelling, and fasciculations occur in such patients. Muscle biopsy specimens show interstitial myositis with destruction of muscle fibers, and pseudocysts of *Toxoplasma gondii* can be found in areas of muscle that are free of inflammatory reaction.[154] It appears that dysregulation of regulatory T cells plays an important role in the development of *Toxoplasma* skeletal muscle involvement.[156]

Other Causes

On occasion, the only clinical manifestations of initial infection with HIV type 1 (HIV-1) are those of polymyositis (myalgias, muscle weakness, and increased serum levels of muscle enzymes).[157] HIV-1 viral antigens can be found in $CD4^+$ T lymphocytes in areas of muscle fiber inflammation and necrosis.[158] During the subsequent course of HIV-1 infection, various forms of muscle disease may develop,[158] including generalized or localized myalgias; HIV myopathy (polymyositis); inclusion body and nemaline myopathies; muscle atrophy accompanying AIDS wasting syndrome or vasculitis; opportunistic infectious myositis, including syphilis[159]; and mitochondrial myopathy related to antiretroviral therapy (see Chapter 128). The clinical presentation of HIV-1 myopathy (inflammatory polymyositis) is that of progressive proximal muscle weakness. It can develop in all stages of the infection and does not correlate with CD4 count.[160] Increased levels of serum creatine phosphokinase and electromyographic changes assist in diagnosis. Muscle biopsy can help resolve this rather long differential diagnosis and guide specific therapy.[158] The inflammatory myopathy may represent primarily an HIV-associated autoimmune process and may respond clinically to prednisone and/or additional immunosuppressive therapies.[157,160]

Inflammatory myositis with a lymphoplasmacytic cellular response has been documented in patients with human T-cell lymphotropic virus-1 (HTLV-1)–associated polymyositis.[161] Muscle-infiltrating $CD8^+$ lymphocytes specific for viral and class I major histocompatibility determinants are present.[137,162] In many areas of highly endemic HTLV-1 infection the majority of patients with polymyositis are HTLV-1 seropositive.[161] There may be a direct toxic effect of HTLV-1 Tax-1 protein on myocytes, even in the absence of myocyte infection.[163] In addition, specific Tax-1 cytotoxic T-lymphocyte activity is present in HTLV-1–infected patients with muscle disease.[163] Inflammatory myositis is rarely

a major feature in Lyme disease[164] and, if present, is often a focal process in relation to adjacent joint or skin involvement. Rarely, a patient presenting with apparent lower extremity pyomyositis actually has Lyme arthritis complicated by a ruptured Baker cyst with a distal intermuscular fluid collection that is positive for *Borrelia burgdorferi* by polymerase chain reaction (PCR) testing. Spirochetes consistent with *B. burgdorferi* may be present on Dieterle silver stain of muscle biopsy specimens, or the presence of *Borrelia* may be confirmed by PCR analysis.[164] Most cases have been reported from Europe, reflecting differences between European and American isolates. Rarely, infection by *Sarcocystis,* an intracellular sporozoan parasite, has been observed in histologic sections of muscle of individuals with muscle pain or weakness, mainly outside the United States.[165] Nematode myositis due to the minute nematode *Haycocknema perplexum* has been observed in Australia.[166] In addition to toxoplasmosis, HIV-infected individuals have developed protozoan myositis due to a variety of microsporidia,[167] including *Trachipleistophora hominis* (see Chapter 268).[168]

PLEURODYNIA SYNDROMES

Epidemic pleurodynia is an acute, febrile disease caused by group B (or rarely by group A) coxsackieviruses that is characterized by the sudden onset of sharp chest pain over the lower ribs or sternum (see Chapter 172). Paroxysms of knifelike pain are precipitated by voluntary or respiratory movements. Muscle tenderness may be present. Abdominal pain may also be present in some patients; in others, abdominal pain may be the sole manifestation, simulating intraperitoneal processes.

Group B coxsackieviruses produce visceral lesions and some focal myositis in experimental animals. Myositis has not been demonstrated as a feature pathologically, either in fatal cases of severe neonatal coxsackievirus B infection or in the few biopsy specimens obtained from affected muscles of patients with epidemic pleurodynia, but it has been associated with rhabdomyolysis complicating mild exercise in the recovery phase of illness.[169] A variety of other enteroviruses rarely provoke rhabdomyolysis.[1] Focal myositis with localized swelling and perivascular mononuclear cell infiltration sparing myocytes was observed in a patient with coxsackievirus A21 infection.[170] Coxsackie B4 has been implicated as a cause of acute myocarditis mimicking influenzal myocarditis.[171]

MYALGIAS WITH EOSINOPHILIA (PARASITIC MYOSITIS)

Trichinosis

Trichinosis is acquired by ingestion of encysted larvae in insufficiently cooked pork or, less commonly, bear meat, wild boar meat, horse meat, or walrus meat. The prominent clinical manifestations of trichinosis include fever, myositis, periorbital edema, and eosinophilia. An initial intestinal phase (nausea, vomiting, nonbloody diarrhea) caused by larval release in the stomach, followed by larval maturation and copulation in the small intestine during the first week, is followed during the second week by release of progeny larvae, mucosal invasion, hematogenous dissemination, and invasion of skeletal muscle (see Chapter 287).[172] Serious complications in the form of myocarditis, meningoencephalitis, and pneumonitis can occur.[172] Myalgias, frequently accompanied by muscle swelling and weakness and occasionally associated with fasciculations, are present in most patients with the disease. Muscles commonly involved include the extraocular muscles, flexor muscles of the extremities, back muscles, and muscles used in chewing and swallowing. Periorbital edema, chemosis, and conjunctival hemorrhages are related to larval invasion of extraocular muscles. The inflammatory response in muscle produces increased serum levels of muscle enzymes and is associated with prominent eosinophilia.

Muscle biopsy specimens reveal encysted larval trichinae in necrotic muscle fibers, surrounded by inflammatory cells (predominantly eosinophils and neutrophils, but also lymphocytes). Severe skeletal muscle involvement reflects the burden of infection and possible host immunosuppression. Although granulomatous reactions have been observed in the heart and lungs in fatal cases, larval encystment does not take place in organs other than skeletal muscle.

Trichinella spiralis is the most common cause of human trichinosis, but multiple other species can infect humans.[172] Unlike *T. spiralis,* *Trichinella pseudospiralis* does not undergo encystment in skeletal muscle and leads to prolonged larval migration and clinical symptoms.

Diagnosis of trichinosis is made on the basis of the clinical picture, eosinophilia, elevated muscle enzymes, compatible serologic findings (enzyme-linked immunosorbent assay, immunoblotting, and, if needed, muscle biopsy), and appropriate epidemiologic investigation.[172] Benzimidazole compounds (thiabendazole, mebendazole, albendazole), which kill mature worms, are the most effective therapies early in the illness; albendazole may have the advantage of being better tolerated. Short courses of systemic corticosteroid therapy ameliorate clinical symptoms and are administered in severe cases.[172]

Trichinosis should be distinguished from the eosinophilia-myalgia syndrome, which results from the ingestion of certain tryptophan products and is characterized by prominent myalgias, fatigue, and eosinophilia, followed, in some instances, by the development of neurologic and scleroderma-like skin changes.[173]

Cysticercosis (*Cysticercus cellulosae* Myositis)

Human cysticercosis is rare in the United States but common in Latin America and Asia. It results from the ingestion and subsequent hatching of viable eggs of *Taenia solium* into the larval form (cysticercus) of the parasite (see Chapter 289). Eggs reach the upper intestinal tract in food contaminated by feces from a person parasitized by the adult worm. Autoinfection can occur through the fecal-oral route and possibly by reverse peristalsis transporting intestinal egg-laden proglottids back into the duodenum or stomach, where they hatch. From the stomach they are widely distributed to the skeletal muscle, subcutaneous tissues, heart, eye, and central nervous system.

Symptomatic involvement of muscle is uncommon. On occasion, the stage of invasion is characterized by fever, muscle tenderness, and eosinophilia, particularly with large inocula.[174] More characteristically, asymptomatic calcified cysts ("puffed rice" appearance) are detected in muscles on soft tissue radiographic films of patients with neurologic manifestations.

MUSCLE DEGENERATION ASSOCIATED WITH INFECTIONS AT OTHER SITES

Acute Rhabdomyolysis

Myoglobinuria occasionally occurs after an acute illness with symptoms suggesting an upper respiratory tract infection and has been associated with a variety of respiratory viral pathogens, including influenza viruses A and B, parainfluenza virus, adenovirus, and severe acute respiratory syndrome–coronavirus, as well as *Mycoplasma pneumoniae* and *Legionella pneumophila.* Rhabdomyolysis has also complicated systemic infections caused by HIV, Epstein-Barr virus, cytomegalovirus, human herpesvirus 6, measles virus, varicella virus, dengue virus, West Nile virus, rabies virus, and parvovirus B19. A variety of bacterial pathogens have led to rhabdomyolysis among critically ill patients with sepsis[175,176]; gram-positive pathogens, including *S. aureus* and *S. pneumoniae,* predominate, but *Salmonella* spp., *Neisseria meningitidis,* and Enterobacteriaceae or nonenteric pathogens, such as *P. aeruginosa* or *Acinetobacter baumannii,* may be responsible. Leptospirosis, brucellosis, and rickettsial infections can also trigger rhabdomyolysis. Diffuse muscle pains (especially in the extremities), weakness, swelling, and tenderness are prominent features, along with increased muscle enzyme (often striking), myoglobinuria, and even acute renal failure.

Muscle Proteolysis and Mediators of Fever in Patients With Sepsis

Muscle involvement in the form of myalgias and weakness is common in the course of systemic infections. Accelerated catabolism of skeletal muscle contributes to the marked weakness and muscle wasting that can be observed in systemic infections. This seems to be part of an acute-phase host response to sepsis and trauma likely triggered by a variety of mediators, including interleukin-1 (IL-1), tumor necrosis factor, interferon-α, and IL-6, as well as endogenously and exogenously administered glucocorticoids. Detailed studies of myocyte mitochondrial number, protein synthesis and expression, mitochondrial enzyme activity,

and messenger RNA levels (including microRNA) in muscle biopsy specimens from septic ICU patients with multiorgan system failure demonstrate a loss of functional mitochondria with sustained but dysregulated mitochondrial protein expression and enhanced proteolytic activity. Transcriptional analysis demonstrated that several critical intracellular pathways (oxidative stress, apoptosis, proteasome function, ion homeostasis, and kinase signaling) are perturbed in these patients.[177]

The intracellular events accompanying muscle catabolism involve prostaglandin E_2 synthesis, direct cleavage of actomyosin by caspase 3,[178] and subsequent degradation by proteasomes. Additional mechanisms also help regulate the process of muscle cachexia.[179] An important role of prostaglandin E_2 in the generation of myalgias and fever is consistent with the amelioration of these symptoms after administration of nonsteroidal antiinflammatory prostaglandin synthesis inhibitors.

Key References

The complete reference list is available online at Expert Consult.

1. Crum-Cianflone NF. Bacterial, fungal, parasitic, and viral myositis. *Clin Microbiol Rev*. 2008;21:473–494.
3. Bickels J, Ben-Sira L, Kessler A, et al. Primary pyomyositis. *J Bone Joint Surg Am*. 2002;84A:2277–2286.
4. Crum NF. Bacterial pyomyositis in the United States. *Am J Med*. 2004;117:420–428.
9. Block AA, Marshall C, Ratcliffe A, et al. Staphylococcal pyomyositis in a temperate region: epidemiology and modern management. *Med J Aust*. 2008;189:323–325.
13. Verma S. Pyomyositis in children. *Curr Infect Dis Rep*. 2016;18:12.
14. Christin L, Sarosi GA. Pyomyositis in North America: case reports and review. *Clin Infect Dis*. 1992;15:668–677.
19. Vassilopoulos D, Chalasani P, Jurado RL, et al. Musculoskeletal infections in patients with human immunodeficiency virus infection. *Medicine (Baltimore)*. 1997;76:284–294.
21. Al-Tawfiq JA, Sarosi GA, Cushing HE. Pyomyositis in the acquired immunodeficiency syndrome. *South Med J*. 2000;93:330–334.
23. Lo TS, Mooers MG, Wright LJ. Pyomyositis complicating acute bacterial endocarditis in an intravenous drug user. *N Engl J Med*. 2000;342:1614–1615.
25. Bocchini CE, Hulten KG, Mason EO Jr, et al. Panton-Valentine leukocidin genes are associated with enhanced inflammatory response and local disease in acute hematogenous *Staphylococcus aureus* osteomyelitis in children. *Pediatrics*. 2006;117:433–440.
28. Schalinski S, Tsokos M. Fatal pyomyositis: a report of 8 autopsy cases. *Am J Forensic Med Pathol*. 2008;29:131–135.
29. Flier S, Dolgin SE, Saphir RL, et al. A case confirming the progressive stages of pyomyositis. *J Pediatr Surg*. 2003;38:1551–1553.
30. Alsoub H. Toxic shock syndrome associated with pyomyositis. *Postgrad Med J*. 1994;70:309.
31. Zervas SJ, Zemel LS, Romness MJ, et al. *Streptococcus pyogenes* pyomyositis. *Pediatr Infect Dis J*. 2002;21:166–168.
32. Al-Najar M, Obeidat F, Ajlouni J, et al. Primary extensive pyomyositis in an immunocompetent patient: case report and literature review. *Clin Rheumatol*. 2010;29:1469–1472.
38. Zadroga RJ, Zylla D, Cawcutt K, et al. Pneumococcal pyomyositis: report of 2 cases and review of the literature. *Clin Infect Dis*. 2012;55:e12–e17.
42. Vigil KJ, Johnson JR, Johnston BD, et al. *Escherichia coli* pyomyositis: an emerging infectious disease among patients with hematologic malignancies. *Clin Infect Dis*. 2010;50:374–380.
47. Brook I. Pyomyositis in children, caused by anaerobic bacteria. *J Pediatr Surg*. 1996;31:394–396.
54. Bonomo RA, Graham R, Makley JT, et al. Tuberculous pyomyositis: an unusual presentation of disseminated *Mycobacterium tuberculosis* infection. *Clin Infect Dis*. 1995;20:1576–1577.
56. Lawn SD, Bicanic TA, Macallan DC. Pyomyositis and cutaneous abscesses due to *Mycobacterium avium:* an immune reconstitution manifestation in a patient with AIDS. *Clin Infect Dis*. 2004;38:461–463.
59. Wysoki MG, Angeid-Backman E, Izes BA. Iliopsoas myositis mimicking appendicitis: MRI diagnosis. *Skeletal Radiol*. 1997;26:316–318.
67. Sauler A, Saul T, Lewiss RE. Point-of-care ultrasound differentiates pyomyositis from cellulitis. *Am J Emerg Med*. 2015;33:482, e3–e5.
69. Tharmarajah H, Marks M. Early use of MRI for suspected pyomyositis. *J Paediatr Child Health*. 2015;51:651–652.
70. Yu JS, Habib P. MR imaging of urgent inflammatory and infectious conditions affecting the soft tissues of the musculoskeletal system. *Emerg Radiol*. 2009;16:267–276.
72. de Araújo BE, Borchert JM, Manhães PG. A rare case of pyomyositis complicated by compartment syndrome caused by ST30-staphylococcal cassette chromosome mec type IV methicillin-resistant *Staphylococcus aureus*. *Am J Emerg Med*. 2010;28:537, e3–e6.
75. Stevens DL. Streptococcal toxic shock syndrome associated with necrotizing fasciitis. *Annu Rev Med*. 2000;51:271–288.
83. Stevens DL, Gibbons AE, Bergstrom R, et al. The Eagle effect revisited: efficacy of clindamycin, erythromycin, and penicillin in the treatment of streptococcal myositis. *J Infect Dis*. 1988;158:23–28.
85. Darenberg J, Ihendyane N, Sjolin J, et al. Intravenous immunoglobulin G therapy in streptococcal toxic shock syndrome: a European randomized, double-blind, placebo-controlled trial. *Clin Infect Dis*. 2003;37:333–340.
86. Johansson L, Thulin P, Low DE, et al. Getting under the skin: the immunopathogenesis of *Streptococcus pyogenes* deep tissue infections. *Clin Infect Dis*. 2010;51:58–65.
90. Altemeier WA, Fullen WD. Prevention and treatment of gas gangrene. *JAMA*. 1971;217:806–813.
95. Bangsberg DR, Rosen JI, Aragon T, et al. Clostridial myonecrosis cluster among injection drug users: a molecular epidemiology investigation. *Arch Intern Med*. 2002;162:517–522.
100. Stevens DL, Musher DM, Watson DA, et al. Spontaneous, non-traumatic gangrene due to *Clostridium septicum*. *Rev Infect Dis*. 1990;12:286–296.
104. Bryant AE. Biology and pathogenesis of thrombosis and procoagulant activity in invasive infections caused by group A streptococci and *Clostridium perfringens*. *Clin Microbiol Rev*. 2003;16:451–462.
105. Stevens DL, Bryant AE. The role of clostridial toxins in the pathogenesis of gas gangrene. *Clin Infect Dis*. 2002;35:S93–S100.
106. Caplan ES, Kluge RM. Gas gangrene: review of 34 cases. *Arch Intern Med*. 1976;136:788–791.
111. Kaide CG, Khandelwal S. Hyperbaric oxygen: applications in infectious disease. *Emerg Med Clin North Am*. 2008;26:571–595.
112. Wang C, Schwaitzberg S, Berliner E, et al. Hyperbaric oxygen for treating wounds: a systematic review of the literature. *Arch Surg*. 2003;138:272–279.
114. Chambers CH, Bond GF, Morris JH. Synergistic necrotizing myositis complicating vascular injury. *J Trauma*. 1974;14:980–984.
117. Bottone EJ. *Bacillus cereus*, a volatile human pathogen. *Clin Microbiol Rev*. 2010;23:382–398.
118. Janda JM, Abbott SL. The genus *Aeromonas:* taxonomy, pathogenicity, and infection. *Clin Microbiol Rev*. 2010;23:35–73.
120. Cone LA, Lamb RB, Graff-Radford A, et al. Pyomyositis of the anterior tibial compartment. *Clin Infect Dis*. 1997;25:146–148.
128. Cronin CG, Gervais DA, Hahn PF, et al. Treatment of deep intramuscular and musculoskeletal abscess: experience with 99 CT-guided percutaneous catheter drainage procedures. *AJR Am J Roentgenol*. 2011;196:1182–1188.
129. Dudler J, Stucki RF, Gerster JC. Aseptic psoas pyomyositis and erosive discitis in a case of calcium pyrophosphate crystal deposition disease. *Rheumatology*. 2000;39:1290–1292.
133. Misra UK, Kalita J, Maurya PK, et al. Dengue-associated transient muscle dysfunction: clinical, electromyography and histopathological changes. *Infection*. 2012;40:125–130.
140. McIntyre PG, Doherty C. Acute benign myositis during childhood: report of five cases. *Clin Infect Dis*. 1995;20:722.
142. Ru YX, Li YC, Zhao Y, et al. Multiple organ invasion by viruses: pathological characteristics in three fatal cases of the 2009 pandemic influenza A/H1N1. *Ultrastruct Pathol*. 2011;35:155–161.
150. González-Juanatey C, Gonzalez-Gay MA, Llorca J, et al. Rheumatic manifestations of infective endocarditis in non-addicts: a 12-year study. *Medicine (Baltimore)*. 2001;80:9–19.
153. Hassene A, Vital A, Anghel A, et al. Acute acquired toxoplasmosis presenting as polymyositis and chorioretinitis in immunocompetent patient. *Joint Bone Spine*. 2008;75:603–605.
164. Holmgren AR, Matteson EL. Lyme myositis. *Arthritis Rheum*. 2006;54:2697–2700.
172. Gottstein B, Pozio E, Nöckler K. Epidemiology, diagnosis, treatment, and control of trichinellosis. *Clin Microbiol Rev*. 2009;22:127–145.
175. Betrosian A, Thireos E, Kofinas G, et al. Bacterial sepsis-induced rhabdomyolysis. *Intensive Care Med*. 1999;25:469–474.

References

1. Crum-Cianflone NF. Bacterial, fungal, parasitic, and viral myositis. *Clin Microbiol Rev*. 2008;21:473–494.
2. Smith IM, Vickers AB. Natural history of 338 treated and untreated patients with staphylococcal septicaemia. *Lancet*. 1960;1:1318–1322.
3. Bickels J, Ben-Sira L, Kessler A, et al. Primary pyomyositis. *J Bone Joint Surg Am*. 2002;84A:2277–2286.
4. Crum NF. Bacterial pyomyositis in the United States. *Am J Med*. 2004;117:420–428.
5. Khoshhal K, Abdelmotaal HM, Alarabi R. Primary obturator internus and obturator externus pyomyositis. *Am J Case Rep*. 2013;14:94–98.
6. Cappellari AM, Borzani IM. Childhood-onset multifocal pyomyositis presenting as critical illness myopathy. *Muscle Nerve*. 2017;55:E22–E23.
7. Fujiwara M, Abe Y, Kodera A, et al. Pyomyositis and osteomyelitis: an unusual cause of abdominal pain. *BMJ Case Rep*. 2018;2018:bcr–2017-223871.
8. Lin MY, Rezai K, Schwartz DN. Septic pulmonary emboli and bacteremia associated with deep tissue infections caused by community-acquired methicillin-resistant *Staphylococcus aureus*. *J Clin Microbiol*. 2008;46:1553–1555.
9. Block AA, Marshall C, Ratcliffe A, et al. Staphylococcal pyomyositis in a temperate region: epidemiology and modern management. *Med J Aust*. 2008;189:323–325.
10. Hsu WC, Hsu JY, Chen MY, et al. Obturator internus pyomyositis manifested as sciatica in a patient with subacute bacterial endocarditis: a rare case report. *Medicine (Baltimore)*. 2016;95:e4340.
11. Horn CV, Master S. Pyomyositis tropicans in Uganda. *East Afr Med J*. 1968;45:463–471.
12. Sharma A, Kumar S, Wanchu A, et al. Clinical characteristics and predictors of mortality in 67 patients with primary pyomyositis: a study from North India. *Clin Rheumatol*. 2010;29:45–51.

12a. Moriarty P, Leung C, Walsh M, et al. Increasing pyomyositis presentations among children in Queensland, Australia. *Pediatr Infect Dis J*. 2015;34:1–4.

13. Verma S. Pyomyositis in children. *Curr Infect Dis Rep*. 2016;18:12.
14. Christin L, Sarosi GA. Pyomyositis in North America: case reports and review. *Clin Infect Dis*. 1992;15:668–677.
15. Rayes AA, Nobre V, Teixeira DM, et al. Tropical pyomyositis and human toxocariasis: a clinical and experimental study. *Am J Med*. 2000;109:422–425.
16. Sokolov KM, Kreye E, Miller LG, et al. Postpartum iliopsoas pyomyositis due to community-acquired methicillin-resistant *Staphylococcus aureus*. *Obstet Gynecol*. 2007;110:535–538.
17. Colmegna I, Justiniano M, Espinoza LR, et al. Piriformis pyomyositis with sciatica: an unrecognized complication of "unsafe" abortions. *J Clin Rheumatol*. 2007;13:87–88.
18. Murray RJ, Pearson JC, Coombs GW, et al. Outbreak of invasive methicillin-resistant *Staphylococcus aureus* infection associated with acupuncture and joint injection. *Infect Control Hosp Epidemiol*. 2008;29:859–865.
19. Vassilopoulos D, Chalasani P, Jurado RL, et al. Musculoskeletal infections in patients with human immunodeficiency virus infection. *Medicine (Baltimore)*. 1997;76:284–294.
20. Heit B, Jones G, Knight D, et al. HIV and other lentiviral infections cause defects in neutrophil chemotaxis, recruitment, and cell structure: immunorestorative effects of granulocyte-macrophage colony-stimulating factor. *J Immunol*. 2006;177:6405–6414.
21. Al-Tawfiq JA, Sarosi GA, Cushing HE. Pyomyositis in the acquired immunodeficiency syndrome. *South Med J*. 2000;93:330–334.
22. Hsueh P-R, Hsiue TR, Hsieh W-C. Pyomyositis in intravenous drug abusers: report of a unique case and review of the literature. *Clin Infect Dis*. 1996;22:858–860.
23. Lo TS, Mooers MG, Wright LJ. Pyomyositis complicating acute bacterial endocarditis in an intravenous drug user. *N Engl J Med*. 2000;342:1614–1615.
24. Miyake H. Beitrag zur Kenntniss des sogenannten Myositis infectiosa. *Mitt Grenzgeb Med Chir*. 1904;13:155.
25. Bocchini CE, Hulten KG, Mason EO Jr, et al. Panton-Valentine leukocidin genes are associated with enhanced inflammatory response and local disease in acute hematogenous *Staphylococcus aureus* osteomyelitis in children. *Pediatrics*. 2006;117:433–440.
26. Kurt K, Rasigade JP, Laurent F, et al. Subpopulations of *Staphylococcus aureus* clonal complex 121 are associated with distinct clinical entities. *PLoS ONE*. 2013;8:e58155.
27. Ray S, Iyer A, Avula S, et al. Acquired torticollis due to primary pyomyositis of the paraspinal muscles in an 11-year-old boy. *BMJ Case Rep*. 2016;2016:bcr2015213409.
28. Schalinski S, Tsokos M. Fatal pyomyositis: a report of 8 autopsy cases. *Am J Forensic Med Pathol*. 2008;29:131–135.
29. Flier S, Dolgin SE, Saphir RL, et al. A case confirming the progressive stages of pyomyositis. *J Pediatr Surg*. 2003;38:1551–1553.
30. Alsoub H. Toxic shock syndrome associated with pyomyositis. *Postgrad Med J*. 1994;70:309.
31. Zervas SJ, Zemel LS, Romness MJ, et al. *Streptococcus pyogenes* pyomyositis. *Pediatr Infect Dis J*. 2002;21:166–168.
32. Al-Najar M, Obeidat F, Ajlouni J, et al. Primary extensive pyomyositis in an immunocompetent patient: case report and literature review. *Clin Rheumatol*. 2010;29:1469–1472.
33. Zhou Z, Song Y, Cai Q, et al. Primary psoas abscess extending to thigh adductors: case report. *BMC Musculoskelet Disord*. 2010;11:176.
34. Young N, Bhally H. Bilateral neck pyomyositis caused by *Staphylococcus capitis* and *Staphylococcus saccharolyticus* in a diabetic adult. *Case Rep Infect Dis*. 2017;2017:3713212.
35. Bhalerao SA, Singh K, Yadav B, et al. Isolated abscess in superior rectus muscle in a child. *Indian J Ophthalmol*. 2015;63:284–286.
36. Kennedy CA, Mathisen G, Goetz MB. Tropical pyomyositis of the abdominal wall musculature mimicking acute abdomen. *West J Med*. 1990;152:296–298.
37. Armstrong JH. Tropical pyomyositis and myoglobinuria. *Arch Intern Med*. 1978;138:1145.
38. Zadroga RJ, Zylla D, Cawcutt K, et al. Pneumococcal pyomyositis: report of 2 cases and review of the literature. *Clin Infect Dis*. 2012;55:e12–e17.
39. Pérez-Rodríguez MT, Sopeña B, Longueira R, et al. Calf pyomyositis caused by *Enterococcus faecalis*. *QJM*. 2011;104:527–529.
40. Yassin M, Yadavalli GK, Alvarado N, et al. *Streptococcus anginosus* (*Streptococcus milleri* group) pyomyositis in a 50-year-old man with acquired immunodeficiency syndrome: case report and review of literature. *Infection*. 2010;38:65–68.
41. Sandlund JT, Howard SC, Hijiya N, et al. Myositis complicating viridans streptococcal sepsis in childhood leukemia. *Pediatr Blood Cancer*. 2005;44:277–279.
42. Vigil KJ, Johnson JR, Johnston BD, et al. *Escherichia coli* pyomyositis: an emerging infectious disease among patients with hematologic malignancies. *Clin Infect Dis*. 2010;50:374–380.
43. Collazos J, Mayo J, Martinez E, et al. Muscle infections caused by *Salmonella* species: case report and review. *Clin Infect Dis*. 1999;29:673–677.
44. Brett ME, Respicio-Kingry LB, Yendell S, et al. Outbreak of *Francisella novicida* bacteremia among inmates at a Louisiana correctional facility. *Clin Infect Dis*. 2014;59:826–833.
45. El-Laboudi AH, Etherington C, Whitaker P, et al. Acute *Burkholderia cenocepacia* pyomyositis in a patient with cystic fibrosis. *J Cyst Fibros*. 2009;8:273–275.
46. Liu AC, Argent JD. Necrobacillosis: a resurgence? *Clin Radiol*. 2002;57:332–338.
47. Brook I. Pyomyositis in children, caused by anaerobic bacteria. *J Pediatr Surg*. 1996;31:394–396.
48. Chan JF, Wong SS, Leung SS, et al. *Capnocytophaga sputigena* primary iliopsoas abscess. *J Med Microbiol*. 2010;59(Pt 11):1368–1370.
49. Zalavras CG, Rigopoulos N, Poultsides L, et al. Increased oxacillin resistance in thigh pyomyositis in diabetic patients. *Clin Orthop Relat Res*. 2008;466:1405–1409.
50. Zhu A, Htet S, Kalro A, et al Breakthrough fusariosis presenting initially.
51. Flagg SD, Chang YJ, Masuell CP, et al. Myositis resulting from disseminated cryptococcosis in a patient with hepatitis C cirrhosis. *Clin Infect Dis*. 2001;32:1104–1107.
52. Goel D, Prayaga AK, Rao N, et al. Histoplasmosis as a cause of nodular myositis in an AIDS patient diagnosed on fine needle aspiration cytology: a case report. *Acta Cytol*. 2007;51:89–91.
53. Schwartz DM, Morgan ER. Multimodality imaging of *Candida tropicalis* myositis. *Pediatr Radiol*. 2008;38:473–476.
54. Bonomo RA, Graham R, Makley JT, et al. Tuberculous pyomyositis: an unusual presentation of disseminated *Mycobacterium tuberculosis* infection. *Clin Infect Dis*. 1995;20:1576–1577.
55. Krishnasamy V, Joseph M. Tuberculous pyomyositis: a rare but serious diagnosis. *Case Rep Med*. 2013;2013:126952.
56. Lawn SD, Bicanic TA, Macallan DC. Pyomyositis and cutaneous abscesses due to *Mycobacterium avium:* an immune reconstitution manifestation in a patient with AIDS. *Clin Infect Dis*. 2004;38:461–463.
57. Jang EY, Lee SO, Choi SH, et al. Case of pyomyositis due to *Mycobacterium haemophilum* in a renal transplant recipient. *J Clin Microbiol*. 2007;45:3847–3849.
58. Pearl GS, Sieger B. Granulomatous *Pneumocystis carinii* myositis presenting as an intramuscular mass. *Clin Infect Dis*. 1996;22:577–578.
59. Wysoki MG, Angeid-Backman E, Izes BA. Iliopsoas myositis mimicking appendicitis: MRI diagnosis. *Skeletal Radiol*. 1997;26:316–318.
60. Chen W-S, Wan Y-L. Iliacus pyomyositis mimicking septic arthritis of the hip joint. *Arch Orthop Trauma Surg*. 1996;115:233–235.
61. Chusid MJ, Hill WC, Bevan JA, et al. *Proteus* pyomyositis of the pyriformis muscle in a swimmer. *Clin Infect Dis*. 1998;26:194–195.
62. Zheng YC, Chen CC, Wei KC, et al. Tropical pyomyositis of erector spinae complicated with spinal epidural abscess. *Clin Neurol Neurosurg*. 2015;128:84–89.
63. Oh GS, Abou-Al-Shaar H, Arnone GD, et al. Spinal epidural abscess in a patient with piriformis pyomyositis. *Surg Neurol Int*. 2016;7(suppl 38):S911–S913.
64. Parmar MS. Diabetic muscle infarction. *BMJ*. 2009;338:171–172.
65. Janga KC, Sinha A, Wengrofsky P, et al. Diabetic muscle infarction masquerading as necrotizing fasciitis. *Case Rep Nephrol*. 2017;2017:7240156.
66. Turecki MB, Taljanovic MS, Stubbs AY, et al. Imaging of musculoskeletal soft tissue infections. *Skeletal Radiol*. 2010;39:957–971.
67. Sauler A, Saul T, Lewiss RE. Point-of-care ultrasound differentiates pyomyositis from cellulitis. *Am J Emerg Med*. 2015;33:482, e3–e5.
68. Kumar MP, Seif D, Perera P, et al. Point-of-care ultrasound in diagnosing pyomyositis: a report of three cases. *J Emerg Med*. 2014;47:420–426.
69. Tharmarajah H, Marks M. Early use of MRI for suspected pyomyositis. *J Paediatr Child Health*. 2015;51:651–652.
70. Yu JS, Habib P. MR imaging of urgent inflammatory and infectious conditions affecting the soft tissues of the musculoskeletal system. *Emerg Radiol*. 2009;16:267–276.
71. Nathan J, Crawford JA, Sodee DB, et al. Fused SPECT/CT imaging of peri-iliopsoas infection using indium-111-labeled leukocytes. *Clin Nucl Med*. 2006;31:801–802.
72. de Araújo BE, Borchert JM, Manhães PG. A rare case of pyomyositis complicated by compartment syndrome caused by ST30-staphylococcal cassette chromosome mec type IV methicillin-resistant *Staphylococcus aureus*. *Am J Emerg Med*. 2010;28:537, e3–e6.
73. Cone LA, Lamb RB, Graff-Radford A, et al. Pyomyositis of the anterior tibial compartment. *Clin Infect Dis*. 1997;25:146–148.
74. Moore DL, Delage G, Labelle H, et al. Peracute streptococcal pyomyositis: report of two cases and review of the literature. *J Pediatr Orthop*. 1986;6:232–235.
75. Stevens DL. Streptococcal toxic shock syndrome associated with necrotizing fasciitis. *Annu Rev Med*. 2000;51:271–288.
76. Stevens DL, Bryant AE. Severe group A streptococcal infections. 2016. In: Ferretti JJ, Stevens DL, Fischetti VA, eds. *Streptococcus pyogenes: Basic Biology to Clinical Manifestations [Internet]*. Oklahoma City (OK): University of Oklahoma Health Sciences Center; 2016.
77. Hourmozdi JJ, Hawley DA, Hadi CM, et al. Streptococcal necrotizing myositis: a case report and clinical review. *J Emerg Med*. 2014;46:436–442.
78. Park S, Shatsky JB, Pawel BR, et al. Atraumatic compartment syndrome: a manifestation of toxic shock and infectious pyomyositis in a child: a case report. *J Bone Joint Surg Am*. 2007;89:1337–1342.
79. Case Records of the Massachusetts General Hospital. Group A beta-hemolytic *Streptococcus* infection, with the compartment and toxic shock syndrome. *N Engl J Med*. 1995;333:113–119.
80. García-Casares E, Mateo Soria L, García-Melchor E, et al. Necrotizing fasciitis and myositis caused by streptococcal flesh-eating bacteria. *J Clin Rheumatol*. 2010;16:382–384.
81. Bruun T, Kittang BR, de Hoog BJ, et al. Necrotizing soft tissue infections caused by *Streptococcus pyogenes* and *Streptococcus dysgalactiae* subsp. *equisimilis* of groups C and G in western Norway. *Clin Microbiol Infect*. 2013;19:E545–E550.
82. Watanabe S, Takemoto N, Ogura K, et al. Severe invasive streptococcal infection by *Streptococcus pyogenes* and *Streptococcus dysgalactiae* subsp. *equisimilis*. *Microbiol Immunol*. 2016;60:1–9.
83. Stevens DL, Gibbons AE, Bergstrom R, et al. The Eagle effect revisited: efficacy of clindamycin, erythromycin, and penicillin in the treatment of streptococcal myositis. *J Infect Dis*. 1988;158:23–28.
84. DeMuri GP, Sterkel AK, Kubica PA, et al. Macrolide and clindamycin resistance in group A streptococci isolated from children with pharyngitis. *Pediatr Infect Dis J*. 2017;36:342–344.
85. Darenberg J, Ihendyane N, Sjolin J, et al. Intravenous immunoglobulin G therapy in streptococcal toxic shock syndrome: a European randomized, double-blind, placebo-controlled trial. *Clin Infect Dis*. 2003;37:333–340.

86. Johansson L, Thulin P, Low DE, et al. Getting under the skin: the immunopathogenesis of *Streptococcus pyogenes* deep tissue infections. *Clin Infect Dis*. 2010;51:58–65.
87. Kadri SS, Swihart BJ, Bonne SL, et al. Impact of intravenous immunoglobulin on survival in necrotizing fasciitis with vasopressor-dependent shock: a propensity score-matched analysis from 130 US hospitals. *Clin Infect Dis*. 2017;64:877–885.
88. Stevens DL, Bryant AE. Necrotizing soft-tissue infections. *N Engl J Med*. 2017;377:2253–2265.
89. Burnham JP, Kirby JP, Kollef MH. Diagnosis and management of skin and soft tissue infections in the intensive care unit: a review. *Intensive Care Med*. 2016;42:1899–1911.
90. Altemeier WA, Fullen WD. Prevention and treatment of gas gangrene. *JAMA*. 1971;217:806–813.
91. MacLennan JD. The histotoxic clostridial infections of man. *Bacteriol Rev*. 1962;26:177–276.
92. Bornstein DL, Weinberg AN, Swartz MN, et al. Anaerobic infections: review of current experience. *Medicine (Baltimore)*. 1964;43:207–232.
93. Stuart Hannah RC, Heddle R, Smith W. Fatal gas gangrene related to self-injection treatment of anaphylaxis. *Ann Allergy Asthma Immunol*. 2011;106:538.
94. Chin RL, Martinez R, Garmel G. Gas gangrene from subcutaneous insulin administration. *Am J Emerg Med*. 1993;11:622–625.
95. Bangsberg DR, Rosen JI, Aragon T, et al. Clostridial myonecrosis cluster among injection drug users: a molecular epidemiology investigation. *Arch Intern Med*. 2002;162:517–522.
96. Kurnutala LN, Ghatol D, Upadhyay A. *Clostridium* sacroiliitis (gas gangrene) following sacroiliac joint injection–case report and review of the literature. *Pain Physician*. 2015;18:E629–E632.
97. McDonald CP, Hartley S, Orchard K, et al. Fatal *Clostridium perfringens* sepsis from a pooled platelet transfusion. *Transfus Med*. 1998;8:19–22.
98. Altemeier WA, Furste WL. Gas gangrene. *Surg Gynecol Obstet*. 1947;84:507–523.
99. Finegold SM. *Anaerobic Bacteria in Human Disease*. New York: Academic Press; 1977:424.
100. Stevens DL, Musher DM, Watson DA, et al. Spontaneous, non-traumatic gangrene due to *Clostridium septicum*. *Rev Infect Dis*. 1990;12:286–296.
101. Lu J, Wu XT, Kong XF, et al. Gas gangrene without wound: both lower extremities affected simultaneously. *Am J Emerg Med*. 2008;26:970, e3–e4.
102. Uzal FA, Freedman JC, Shrestha A, et al. Towards an understanding of the role of *Clostridium perfringens* toxins in human and animal disease. *Future Microbiol*. 2014;9:361–377.
103. Stevens DL, Tweten RK, Awad MM, et al. Clostridial gas gangrene: evidence that α and θ toxins differentially modulate the immune response and induce acute tissue necrosis. *J Infect Dis*. 1997;176:189–195.
104. Bryant AE. Biology and pathogenesis of thrombosis and procoagulant activity in invasive infections caused by group A streptococci and *Clostridium perfringens*. *Clin Microbiol Rev*. 2003;16:451–462.
105. Stevens DL, Bryant AE. The role of clostridial toxins in the pathogenesis of gas gangrene. *Clin Infect Dis*. 2002;35:S93–S100.
106. Caplan ES, Kluge RM. Gas gangrene: review of 34 cases. *Arch Intern Med*. 1976;136:788–791.
107. Dylewski J, Wiesenfeld H, Latour A. Postpartum uterine infection with *Clostridium perfringens*. *Rev Infect Dis*. 1989;11:470–473.
108. Stevens DL, Maier KA, Laine BM, et al. Comparison of clindamycin, rifampin, tetracycline, metronidazole, and penicillin for efficacy in prevention of experimental gas gangrene due to *Clostridium perfringens*. *J Infect Dis*. 1987;155:220–228.
109. Stevens DL, Laine BM, Mitten JE. Comparison of single and combination antimicrobial agents for prevention of experimental gas gangrene caused by *Clostridium perfringens*. *Antimicrob Agents Chemother*. 1987;31:312–316.
110. Roberts SA, Shore KP, Paviour SD, et al. Antimicrobial susceptibility of anaerobic bacteria in New Zealand: 1999-2003. *J Antimicrob Chemother*. 2006;57:992–998.
111. Kaide CG, Khandelwal S. Hyperbaric oxygen: applications in infectious disease. *Emerg Med Clin North Am*. 2008;26:571–595.
112. Wang C, Schwaitzberg S, Berliner E, et al. Hyperbaric oxygen for treating wounds: a systematic review of the literature. *Arch Surg*. 2003;138:272–279.
113. Stevens DL, Bryant AE, Adams K, et al. Evaluation of therapy with hyperbaric oxygen for experimental infection with *Clostridium perfringens*. *Clin Infect Dis*. 1993;17:231–237.
114. Chambers CH, Bond GF, Morris JH. Synergistic necrotizing myositis complicating vascular injury. *J Trauma*. 1974;14:980–984.
115. Bruno-Murtha LA, Sedghivaziri MA, Arbeit RD. Crepitant myonecrosis caused by *Klebsiella pneumoniae* in an immunocompromised diabetic patient. *J Infect Dis*. 1990;162:1415–1416.
116. Fata F, Chittivelu S, Tessler S, et al. Gas gangrene of the arm due to *Enterobacter cloacae* in a neutropenic patient. *South Med J*. 1996;89:1095–1096.
117. Bottone EJ. *Bacillus cereus,* a volatile human pathogen. *Clin Microbiol Rev*. 2010;23:382–398.
118. Janda JM, Abbott SL. The genus *Aeromonas:* taxonomy, pathogenicity, and infection. *Clin Microbiol Rev*. 2010;23:35–73.
119. Papadakis V, Poniros N, Katsibardi K, et al. Fulminant *Aeromonas hydrophila* infection during acute lymphoblastic leukemia treatment. *J Microbiol Immunol Infect*. 2012;45:154–157.
120. Cone LA, Lamb RB, Graff-Radford A, et al. Pyomyositis of the anterior tibial compartment. *Clin Infect Dis*. 1997;25:146–148.
121. Mallick IH, Thoufeeq MH, Rajendran TP. Iliopsoas abscesses. *Postgrad Med J*. 2004;80:459–462.
122. Shields D, Robinson P, Crowley TP. Iliopsoas abscess—a review and update on the literature. *Int J Surg*. 2012;10:466–469.
123. Shahabi S, Klein JP, Rinaudo PF. Primary psoas abscess complicating a normal vaginal delivery. *Obstet Gynecol*. 2002;99:906–909.
124. Yang JY, Lee JK, Cha SM, Joo YB. Psoas abscess caused by spontaneous rupture of colon cancer. *Clin Orthop Surg*. 2011;3:342–344.
125. Simons GW, Sty JR, Starshak RJ, et al. Retroperitoneal and retrofascial abscesses. *J Bone Joint Surg Am*. 1983;65A:1041–1058.
126. Zissin R, Gayer G, Kots E, et al. Iliopsoas abscess: a report of 24 patients diagnosed by CT. *Abdom Imaging*. 2001;26:533–539.
127. Takada T, Terada K, Kajiwara H, et al. Limitations of using imaging diagnosis for psoas abscess in its early stage. *Intern Med*. 2015;54:2589–2593.
128. Cronin CG, Gervais DA, Hahn PF, et al. Treatment of deep intramuscular and musculoskeletal abscess: experience with 99 CT-guided percutaneous catheter drainage procedures. *AJR Am J Roentgenol*. 2011;196:1182–1188.
129. Dudler J, Stucki RF, Gerster JC. Aseptic psoas pyomyositis and erosive discitis in a case of calcium pyrophosphate crystal deposition disease. *Rheumatology*. 2000;39:1290–1292.
130. Breda L, Di Michele S, de Michele G, et al. Obturator internus muscle abscess mimicking septic arthritis of the hip. *Clin Rheumatol*. 2006;25:608–609.
131. Hernandez RJ, Strouse PJ, Craig CL, et al. Focal pyomyositis of the perisciatic muscles in children. *AJR Am J Roentgenol*. 2002;179:1267–1271.
132. Borgatta B, Pérez M, Rello J, et al. Elevation of creatine kinase is associated with worse outcomes in 2009 pH1N1 influenza A infection. *Intensive Care Med*. 2012;38:1152–1161.
133. Misra UK, Kalita J, Maurya PK, et al. Dengue-associated transient muscle dysfunction: clinical, electromyography and histopathological changes. *Infection*. 2012;40:125–130.
134. Hu JJ, Kao CL, Lee PI, et al. Clinical features of influenza A and B in children and association with myositis. *J Microbiol Immunol Infect*. 2004;37:95–98.
135. Mall S, Buchholz U, Tibussek D, et al. A large outbreak of influenza B-associated benign acute childhood myositis in Germany, 2007/2008. *Pediatr Infect Dis J*. 2011;30:e142–e146.
136. Morton SE, Mathai M, Byrd RP Jr, et al. Influenza A pneumonia with rhabdomyolysis. *South Med J*. 2001;94:67–69.
137. Saito M, Higuchi I, Saito A, et al. Molecular analysis of T cell clonotypes in muscle-infiltrating lymphocytes from patients with human T lymphotropic virus type 1 polymyositis. *J Infect Dis*. 2002;186:1231–1241.
138. Bach JF. Infections and autoimmune diseases. *J Autoimmun*. 2005;25(suppl):74–80.
139. Sellers SA, Hagan RS, Hayden FG, et al. The hidden burden of influenza: a review of the extra-pulmonary complications of influenza infection. *Influenza Other Respir Viruses*. 2017;11:372–393.
140. McIntyre PG, Doherty C. Acute benign myositis during childhood: report of five cases. *Clin Infect Dis*. 1995;20:722.
141. Slobogean BL, Reilly CW, Alvarez CM. Recurrent viral-induced compartment syndrome. *Pediatr Emerg Care*. 2011;27:660–662.
142. Ru YX, Li YC, Zhao Y, et al. Multiple organ invasion by viruses: pathological characteristics in three fatal cases of the 2009 pandemic influenza A/H1N1. *Ultrastruct Pathol*. 2011;35:155–161.
143. Magee H, Goldman RD. Viral myositis in children. *Can Fam Physician*. 2017;63:365–368.
144. Rezkalla SH, Kloner RA. Influenza-related viral myocarditis. *WMJ*. 2010;109:209–213.
145. Levenson JE, Kaul DR, Saint S, et al. Clinical problem-solving. A shocking development. *N Engl J Med*. 2013;369:2253–2258.
146. Taremi M, Amoroso A, Nace HL, et al. Influenza B-induced refractory cardiogenic shock: a case report. *BMC Infect Dis*. 2013;13:452.
147. Lefeuvre C, Behillil S, Triau S, et al. Fatal myopericarditis following an influenza A (H3N2) infection. *Am J Case Rep*. 2018;19:540–544.
148. Estabragh ZR, Mamas MA. The cardiovascular manifestations of influenza: a systematic review. *Int J Cardiol*. 2013;167:2397–2403.
149. Buzon J, Roignot O, Lemoine S, et al. Takotsubo Cardiomyopathy triggered by influenza A virus. *Intern Med*. 2015;54:2017–2019.
150. González-Juanatey C, Gonzalez-Gay MA, Llorca J, et al. Rheumatic manifestations of infective endocarditis in non-addicts: a 12-year study. *Medicine (Baltimore)*. 2001;80:9–19.
151. Ojeda J, López-López L, González A, et al. Infective endocarditis initially presenting with a dermatomyositis-like syndrome. *BMJ Case Rep*. 2014;2014:pii:bcr2013200865.
152. Georgescu AM, Azamfirei L, Szalman K, et al. Fatal endocarditis with methicillin-sensible *Staphylococcus aureus* and major complications: rhabdomyolysis, pericarditis, and intracerebral hematoma: a case report and review of the literature. *Medicine (Baltimore)*. 2016;95:41. (e5125).
153. Hassene A, Vital A, Anghel A, et al. Acute acquired toxoplasmosis presenting as polymyositis and chorioretinitis in immunocompetent patient. *Joint Bone Spine*. 2008;75:603–605.
154. Gherardi R, Baudrimont M, Lionnet F, et al. Skeletal muscle toxoplasmosis in patients with acquired immunodeficiency syndrome: a clinical and pathological study. *Ann Neurol*. 1992;32:535–542.
155. Plonquet A, Bassez G, Authier FJ, et al. Toxoplasmic myositis as a presenting manifestation of idiopathic CD4 lymphocytopenia. *Muscle Nerve*. 2003;27:761–765.
156. Wohlfert EA, Blader IJ, Wilson EH. Brains and Brawn: *Toxoplasma* infections of the central nervous system and skeletal muscle. *Trends Parasitol*. 2017;33:519–531.
157. Lloyd TE, Pinal-Fernandez I, Michelle EH, et al. Overlapping features of polymyositis and inclusion body myositis in HIV-infected patients. *Neurology*. 2017;88:1454–1460.
158. Authier FJ, Chariot P, Gherardi RK. Skeletal muscle involvement in human immunodeficiency virus (HIV)-infected patients in the era of highly active antiretroviral therapy (HAART). *Muscle Nerve*. 2005;32:247–260.
159. Yacyshyn E, Chiowchanwisawakit P, Emery DJ, et al. Syphilitic myositis: a case-based review. *Clin Rheumatol*. 2011;30:729–733.
160. Virot E, Duclos A, Adelaide L, et al. Autoimmune diseases and HIV infection: a cross-sectional study. *Medicine (Baltimore)*. 2017;96:4 (e5769.
161. McKendall RR. Neurologic disease due to HTLV-1 infection. *Handb Clin Neurol*. 2014;123:507–530.
162. Desdouits M, Cassar O, Maisonobe T, et al. HTLV-1-associated inflammatory myopathies: low proviral load and moderate inflammation in 13 patients from West Indies and West Africa. *J Clin Virol*. 2013;57:70–76.
163. Ozden S, Mouly V, Prevost MC, et al. Muscle wasting induced by HTLV-1 tax-1 protein: an in vitro and in vivo study. *Am J Pathol*. 2005;167:1609–1619.
164. Holmgren AR, Matteson EL. Lyme myositis. *Arthritis Rheum*. 2006;54:2697–2700.
165. Fayer R, Esposito DH, Dubey JP. Human infections with *Sarcocystis* species. *Clin Microbiol Rev*. 2015;28:295–311.
166. Vos LJ, Robertson T, Binotto E. *Haycocknema perplexum:* an emerging cause of parasitic myositis in Australia. *Commun Dis Intell Q Rep*. 2016;40:E496–E499.
167. Kotler DP, Orenstein JM. Clinical syndromes associated with microsporidiosis. *Adv Parasitol*. 1998;40:321–349.
168. Curry A, Beeching NJ, Gilbert JD, et al. *Trachipleistophora hominis* infection in the myocardium and skeletal muscle of a patient with AIDS. *J Infect*. 2005;51:e139–e144.
169. Marinella MA. Exertional rhabdomyolysis after recent coxsackie B virus infection. *South Med J*. 1998;91:1057–1059.
170. Dekel B, Yoeli R, Shulman L, et al. Localized thigh swelling mimicking a neoplastic process: involvement of coxsackie virus type A21. *Acta Paediatr*. 2002;91:357–359.
171. Ikeda T, Saito T, Takagi G, et al. Acute myocarditis associated with coxsackievirus B4 mimicking influenza

myocarditis: electron microscopy detection of causal virus of myocarditis. *Circulation*. 2013;128:2811–2812.
172. Gottstein B, Pozio E, Nöckler K. Epidemiology, diagnosis, treatment, and control of trichinellosis. *Clin Microbiol Rev*. 2009;22:127–145.
173. Culpepper RC, Williams RG, Mease PJ, et al. Natural history of the eosinophilia-myalgia syndrome. *Ann Intern Med*. 1991;115:437–442.
174. Meng Q, Liu L. Disseminated cysticercosis. *N Engl J Med*. 2016;375:e52.
175. Betrosian A, Thireos E, Kofinas G, et al. Bacterial sepsis-induced rhabdomyolysis. *Intensive Care Med*. 1999;25:469–474.
176. Kumar AA, Bhaskar E, Palamaner Subash Shantha G, et al. Rhabdomyolysis in community acquired bacterial sepsis—a retrospective cohort study. *PLoS ONE*. 2009;4:e7182.
177. Fredriksson K, Tjäder I, Keller P, et al. Dysregulation of mitochondrial dynamics and the muscle transcriptome in ICU patients suffering from sepsis induced multiple organ failure. *PLoS ONE*. 2008;3:e3686.
178. Du J, Wang X, Miereles C, et al. Activation of caspase-3 is an initial step triggering accelerated muscle proteolysis in catabolic conditions. *J Clin Invest*. 2004;113:115–123.
179. Pajak B, Orzechowska S, Pijet B, et al. Crossroads of cytokine signaling—the chase to stop muscle cachexia. *J Physiol Pharmacol*. 2008;59(suppl 9):251–264.

95 Lymphadenitis and Lymphangitis

Mark S. Pasternack

SHORT VIEW SUMMARY

Definition: Lymphadenitis
- Acute (suppurative) or chronic (often granulomatous) inflammation of the lymph nodes

Epidemiology
- Suppurative lymphadenitis most common among young children; granulomatous lymphadenitis may occur in individuals of all ages

Microbiology (see Table 95.1)
- Suppurative lymphadenitis is due primarily to *Staphylococcus aureus* (methicillin sensitive and methicillin resistant) and group A streptococci in normal hosts; a variety of pathogens may cause suppurative lymphadenitis in immunocompromised individuals.
- Granulomatous lymphadenitis is due primarily to nontuberculous mycobacteria in healthy children. *Mycobacterium tuberculosis* is the most important etiology in older patients, but it may be due to a variety of pathogens in compromised hosts.

Diagnosis
- Needle aspiration, incisional biopsy, or excisional biopsy, depending on the tempo and severity of the illness and possible immunodeficiency

Therapy
- Drainage of established abscesses and conventional antimicrobial therapy against gram-positive pathogens for acute suppurative lymphadenitis
- Targeted therapy based on microbiologic/histopathologic investigation for chronic granulomatous lymphadenitis

Prevention
- Early therapy of primary superficial infections and early therapy of acute adenitis episodes may reduce the risk of suppuration and need for surgical drainage.

Definition: Lymphangitis
- Lymphangitis is an inflammation of lymphatic channels, usually in subcutaneous tissues. It is caused by an acute process of bacterial origin or as a chronic process of mycotic, mycobacterial, or filarial etiology (see Table 95.2).

LYMPHADENITIS

Lymphadenitis is an acute or chronic inflammation of lymph nodes. It may be restricted to a solitary node or to a localized group of nodes draining an anatomic area (regional lymphadenitis), or the involvement can be generalized during a systemic infection. The gross features may reflect nonsuppurative, suppurative, necrotizing, or caseous inflammation, depending on the nature of the infecting microorganism, or noninfectious inflammatory or neoplastic processes. Fine-needle aspiration cytology is often a valuable minimally invasive diagnostic procedure, although it occasionally may be complicated by sinus tract formation in patients with granulomatous lymphadenitis.[1]

Pathogenesis and Pathologic Changes

Acute Lymphadenitis

Lymph nodes serve as filters, removing infectious agents from lymphatics draining areas of acute inflammation. The initial histologic response consists of swelling and hyperplasia of sinusoidal lining cells and the infiltration of leukocytes. Depending on the nature of the infecting organism, host defenses, and antimicrobial therapy, the process may or may not progress to abscess formation. With some microorganisms, a more distinctive pathologic picture may be seen: granulomas and caseation necrosis with infections due to *Mycobacterium tuberculosis* and nontuberculous mycobacteria; stellate abscesses surrounded by palisading epithelioid cells (granulomatous abscess)[2] with lymphogranuloma venereum (LGV), cat-scratch disease, tularemia, yersiniosis, fungal lymphadenitis, and chronic granulomatous disease; or reactive follicular hyperplasia with scattered clusters of epithelioid histiocytes characteristically blurring the margins of germinal centers, along with focal distention of subcapsular and trabecular sinuses by monocytoid B cells, in toxoplasmosis.[3] The necrotizing granulomatous lymphadenitis that occurs in tularemia can resemble that occurring in cat-scratch disease but often exhibits more granulomatous inflammation. *Yersinia* (*Yersinia pseudotuberculosis* or *Yersinia enterocolitica*) infection in mesenteric lymph nodes can also cause a necrotizing lymphadenitis. Necrotizing nongranulomatous lymphadenitis may be a feature of processes to which an infectious cause has not yet been ascribed: Kikuchi necrotizing lymphadenitis, Kawasaki disease, and systemic lupus erythematosus.[4] Necrotizing viral lymphadenitis has been documented to be due to herpes simplex virus, primarily in individuals with underlying hematologic disorders,[5] cowpox,[6] parvovirus B19,[7] and human herpesvirus 6 (HHV-6)[8] in healthy individuals, as well as in patients with systemic lupus erythematosus.

Chronic Lymphadenitis

Histologically, the response is proliferative with hyperplasia of reticuloendothelial cells, prominent germinal centers, and dilated lymph sinuses filled with mononuclear cells. This nonspecific picture can be seen with a variety of infections and may be observed initially on biopsy in a patient subsequently proven to have a lymphoproliferative disorder. Noncaseous granulomatous lymphadenitis is characteristic of sarcoidosis. More destructive granulomatous lymphadenitis with necrosis or caseation may occur in tuberculous or fungal lymphadenitis, particularly histoplasmosis.

Dermatopathic lymphadenitis (lipomelanotic reticuloendotheliosis) is a distinctive form of chronic lymphadenitis involving lymph nodes draining sites of chronic pruritic dermatitides. These enlarged nodes characteristically demonstrate accumulation of lipid and melanin in macrophages derived from the cutaneous inflammatory process. The hyperplastic appearance of such nodes may be so prominent as to suggest erroneously a lymphoproliferative disorder. Similarly, inflammatory pseudotumor can present with progressive cervical lymphadenopathy with systemic symptoms and thus mimic tuberculosis (TB) or lymphoma.

Clinical Manifestations

Acute Regional Lymphadenitis Due to Pyogenic Bacteria

Palpable lymph nodes do not always indicate serious or ongoing disease. Some degree of inguinal lymphadenopathy is relatively common, reflecting previous episodes of infection in the lower extremities (e.g., interdigital web infections secondary to dermatophytosis); similarly,

slight enlargement of cervical nodes may persist from previous pharyngeal or dental infections. Lymphadenopathy in certain anatomic areas (preauricular, posterior auricular, supraclavicular, deltoideopectoral, and pectoral) should always be viewed with greater suspicion because these nodes are not frequently enlarged as a result of local subclinical infections or minor trauma. Enlargement of superficial lymph nodes along the external jugular vein, as well as of nodes that drain the earlobe and the floor of the external acoustic meatus, may be associated with superficial infection accompanying recent ear piercing. Rarely, a firm mass in the tail or lateral aspect of the breast, suggestive of carcinoma, proves to be an enlarged lymph node in an unusual location caused by toxoplasmosis.[3]

Acute suppurative lymphadenitis is far more common in children than in adults. In the past 4 decades *Staphylococcus aureus* (both methicillin-susceptible and methicillin-resistant strains[9,10]) has superseded group A streptococci as the most frequent etiologic agent. The most common sites of involvement are, in descending order, submandibular (submaxillary), anterior and posterior cervical, inguinal, and axillary lymph nodes. The portal of entry for infection is frequently difficult to determine in children when cervical lymph nodes are involved. The recovery of a variety of anaerobic pathogens and/or α-hemolytic streptococci, including *Streptococcus intermedius*[11] in cervical lymph node aspirates from some patients, suggests that in addition to cutaneous foci, primary dental or pharyngeal infections may lead to suppurative lymphadenitis.[12,13]

On examination the involved area is swollen, and the node(s) are usually at least 3 cm in diameter and tender. Fever is commonly present. The node(s) may be firm or frankly fluctuant. The overlying skin is warm and often erythematous and edematous.

Syndromes Due to Suppurative Lymphadenitis at Specific Anatomic Sites

Cervical Lymphadenitis

Acute unilateral adenitis of pyogenic origin occurs most often in preschool-age children; bilateral disease occurs in less than 10% of cases.[10] Fever (38°C–39°C) is common, and local swelling is often present for some days before the patient is seen by a physician. Although in only a minority of cases is there a history of sore throat, group A streptococci historically have been the most common cause of suppurative cervical lymphadenitis in children. *S. aureus* or a combination of *S. aureus* and group A streptococci is often responsible for suppurative cervical lymphadenitis associated with pyodermas of the face and scalp. Improved anaerobic culture techniques have demonstrated a variety of oral anaerobes in percutaneous needle aspirates in up to 40% of patients, as either pure anaerobic infections or mixed infections with conventional gram-positive aerobes.[12,13] Acute torticollis may result from cervical lymphadenitis of either bacterial or viral (e.g., infectious mononucleosis) origin and may be the initial symptom that brings the child to the physician.[14] Cervical lymphadenitis associated with torticollis may also indicate the presence of associated retropharyngeal and/or parapharyngeal space infection.[15]

On examination there is prominent swelling of the neck or face owing to the enlargement of a single node or a matted collection of adjacent lymph nodes, which may be walnut sized. The mass is typically exquisitely tender and firm at presentation but may be fluctuant initially or develop fluctuance during the course of therapy. The swelling may be sufficiently marked to limit mouth opening or evoke trismus. A white blood cell count of 12,000 to 25,000/mm^3 is common. Drainable suppurative lymphadenitis may develop in up to 20% of acute cervical lymphadenitis episodes, particularly in younger children with unilateral disease and symptom duration over 48 hours.[16]

Acute bilateral cervical adenitis usually involves multiple nodes that are enlarged and somewhat tender in association with viral pharyngitis, infectious mononucleosis and related syndromes, HHV-6,[8,17] streptococcal pharyngitis, or periodontal infection. Such lymphadenopathy may progress to suppuration if the primary pyogenic process is untreated. Bilateral suppurative lymphadenitis may occur at increased frequency in immunocompromised hosts (e.g., chronic granulomatous disease).[18]

Acute Axillary Lymphadenitis

This process, when due to *Streptococcus pyogenes,* is characterized by an abrupt onset with chills, fever, marked axillary pain, and prominent edema of the shoulder, arm, axilla, supraclavicular fossa, and pectoral areas.[19] The site of initiating infection is usually a pustule or traumatic lesion on the hand or arm. The involved area, although edematous, does not have features of cellulitis, lymphangitis, or erysipelas. Ipsilateral pleural effusion may develop due to blockage of lymphatic vessels draining the parietal pleura into the involved lymph nodes at the junction of the internal jugular and subclavian veins. Thrombosis of the axillary and subclavian veins may be a complication. In countries where infants are routinely inoculated with Calmette-Guérin bacillus (BCG), acute axillary lymphadenitis ipsilateral to the BCG inoculation site is occasionally seen[2,20] and, if severe, may implicate significant underlying immunodeficiency.[21]

Subpectoral Lymphadenitis

An unusual course may be taken occasionally by infection (usually streptococcal but sometimes staphylococcal) of the thumb or the interdigital web between the thumb and index finger. Lymphatics from this area do not pass through the epitrochlear nodes but drain directly into the axillary nodes, which in turn communicate with the subpectoral nodes. If infection is not contained in the axillary nodes, subpectoral lymphadenitis develops and may progress to frank suppuration. Infection in this area may dissect downward and manifest as cellulitis over the lower chest and upper abdomen, suggesting an intraabdominal infection. On occasion, large subpectoral abscesses may suggest a tumor because the overlying pectoralis major obscures the local warmth and erythema commonly associated with infection. Rarely, contraction of the pectoral muscle (as on arm elevation) causes movement of the pectoral area swelling, suggesting avulsion of the inferior attachments of this muscle. The suppurating nodes may drain onto the chest wall. Pleural effusion may develop on the involved side.

Deep Neck Space Lymphadenitis

The development of progressive parapharyngeal or retropharyngeal infection complicating primary intraoral infection may become a life-threatening complication due to progressive inflammation, necrosis, or abscess formation, or a combination of these, compromising vital neck structures and the mediastinum (see Chapter 85). Computed tomography (CT) has been invaluable to localize these infections and guide surgical management, but in some cases, focal low-density abnormalities that do not yield drainable pus at exploration are identified.[22,23] In these cases focal parapharyngeal[23] or retropharyngeal lymphadenitis,[22] recognizable by its relatively small size or relatively posterior location in the parapharyngeal space, may account for these radiologic abnormalities and be amenable to nonsurgical management with antibiotic therapy and close follow-up. Acute cervical lymphadenitis may be present in association with these deep-space infections and may represent the presenting complaint, leading to initial evaluation.[15]

Acute Mediastinal Lymphadenitis

Acute suppurative mediastinal lymphadenitis is usually recognized in the course of managing bacterial mediastinitis, a fulminant process typically complicating progressive infections of the upper respiratory tract or perforation of the esophagus or bronchial tree as the result of trauma or surgery. Rarely, odontogenic foci of infection may lead to progressive mediastinal lymphadenitis without apparent progressive infection of the head and neck. Suppurative mediastinal lymphadenitis may result in the superior vena cava syndrome.[24] The superior vena cava syndrome has also been attributed to marked reactive lymphadenopathy in the setting of cystic fibrosis without frank mediastinal suppuration.[25] Prominent acute hemorrhagic thoracic lymphadenitis is a feature of inhalation anthrax, an aspect reemphasized in the 2001 bioterrorism-related anthrax outbreak.[26]

Acute Suppurative Epitrochlear Lymphadenitis

The epitrochlear nodes receive lymphatic drainage from the middle, ring, and little fingers and from the medial portion of the hand and the ulnar aspect of the forearm. Acute suppurative epitrochlear

lymphadenitis is uncommon and generally accompanies a primary pyoderma or a secondarily infected skin lesion. Unilateral tender swelling, erythema, and induration of the epitrochlear area develop and may subsequently spread along the medial aspect of the arm and forearm. There is often pain on elbow movement, moderate fever, and leukocytosis. The diagnosis is apparent when a discrete, tender nodular swelling can be palpated, but when the area is diffusely swollen and movement at the elbow is limited, the picture may suggest septic arthritis, osteomyelitis, subcutaneous abscess, or olecranon bursitis, and ultrasound may help to clarify the diagnosis.[27,28] Group A streptococci and *S. aureus* are implicated most commonly. In contrast, cat-scratch disease and TB involving the epitrochlear lymph nodes present in a more indolent fashion.

Suppurative Iliac Lymphadenitis

The iliac lymph nodes, located along the external and common iliac arteries in the anterior retroperitoneal space, receive lymphatic drainage from the lower abdominal wall and the superficial and deep inguinal nodes. Iliac lymphadenitis may develop secondary to infection of the lower extremities, lower abdominal wall, or perineum, or rarely may result from hematogenous infection. After infection develops, it appears to break through fascial compartments in the iliac fossa, and abscess formation ensues. Formerly, most cases occurred in children and young adults, but more recently there seems to be no age predilection. The suppurative lymphadenitis progresses to abscess formation in the space between the posterior peritoneum and the psoas and iliacus fascia.[29] Patients may present with an unexplained limp without systemic symptoms, followed by back and hip pain. Although extension of the thigh is painful, abduction and adduction of the hip evoke minimal discomfort. The symptomatology and clinical findings suggest possible septic arthritis and osteomyelitis. Only after some days or weeks does lower abdominal pain develop, and the patient becomes acutely ill with high fever and marked leukocytosis. Patients may demonstrate a tightly flexed hip, ipsilateral rectus muscle spasm, or possibly a tender posterolateral pelvic mass or a tender inguinal mass suggesting an incarcerated inguinal hernia. By this stage the abscess may be sizable and displace the sigmoid colon or the lower third of the ureter, or both. Right-sided symptoms suggest the diagnosis of *retrocecal* appendicitis with abscess, ischemic colitis, or cecal carcinoma, but the antecedent limp is an important clinical clue. TB of the spine with psoas abscess formation, pelvic inflammatory disease, and tumor of the thigh should also be considered.[30] Tuberculous (BCG) iliac lymphadenitis has also been reported after intravesical BCG instillation for the treatment of bladder carcinoma.[31] Cross-sectional imaging (CT or magnetic resonance imaging) can be helpful in defining an inflammatory collection abutting the psoas and iliacus muscles and narrowing the differential diagnosis.[32] *S. aureus* is the microorganism most commonly implicated, followed in frequency by streptococci. Rarely, noninfectious processes such as Kikuchi-Fujimoto disease may present with fever and prominent iliac lymphadenopathy mimicking suppurative iliac lymphadenitis.[33]

Acute Regional Lymphadenitis Due to Infecting Agents Other Than Pyogenic Bacteria

A variety of organisms other than the common pyogenic ones may produce localized lymphadenitis, in some cases going on to abscess and sinus tract formation. These infections are generally distinguishable by a prolonged and indolent course, the atypical anatomic areas involved, the lack of previous superficial pyogenic infection, and sometimes by additional clues in the history and epidemiology (e.g., cat scratch, previous TB, travel history, recent sexual exposures, clinical setting, underlying host immunodeficiency). Syphilitic cervical lymphadenopathy presents subacutely with painless firm prominent adenopathy and may be accompanied by an oral chancre, aiding in the clinical diagnosis, but may be an obscure diagnosis in the absence of oropharyngeal ulceration.[34] Clinical suspicion of syphilis should lead to serologic confirmation of the diagnosis, but excisional biopsy and demonstration of "starry sky" histologic features with prominent plasma cell infiltration, occlusive capillaritis, and endothelial swelling,[35] as well as the presence of spirochetes using Warthin-Starry staining,[36] may confirm the diagnosis when the prebiopsy probability is low. Advanced imaging techniques, such as ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET)-CT scanning, has identified *Coxiella burnetii* lymphadenitis as a focal infection or in association with deep parenchymal infection in patients diagnosed with chronic Q fever.[37,38] Cowpox can cause ulcerating lesions in unimmunized individuals that are associated with regional lymphadenopathy and may mimic ulceroglandular tularemia and (less likely) plague.[38a]

A broad spectrum of microorganisms must be considered as the cause of firm or fluctuant lymphadenitis when evaluating compromised hosts. Actinomycotic lymphadenitis may occur in normal and immunocompromised hosts.[39] Mycotic (*Candida albicans, Aspergillus* spp.) cervical lymphadenitis has occurred after oral mucositis in neutropenic children[40] and adults[41] with leukemia, but a rare case of bilateral cervical lymphadenopathy due to *Aspergillus fumigatus* was described in a young girl without underlying disease, neutropenia, or immunosuppression.[42] Cryptococcal lymphadenitis has also been observed in apparently normal hosts.[43] Acquired immunodeficiency due to the development of autoantibodies against interferon-γ (anti–IFN-γ) has been identified among some Asian and African individuals. This may underlie some cases of opportunistic infections, including nontuberculous mycobacterial lymphadenitis, in previously apparently normal hosts carrying selected human leukocyte antigen DR and DQ alleles.[44] Necrotizing cervical lymphadenitis due to *Histoplasma capsulatum* was observed in a woman of African descent with anti–IFN-γ antibodies.[45] In patients with suppurative lymphadenitis complicating chronic granulomatous disease, the microbial etiology is usually a catalase-positive pathogen.[46] In addition to the commonly involved *S. aureus,* these include members of the family Enterobacteriaceae *(Klebsiella, Serratia, Salmonella), Pseudomonas* or *Burkholderia cepacia*, *Aspergillus, Nocardia,* BCG,[47] *Chromobacterium violaceum, Rothia aeria,*[48] and Acetobacteraceae-related agents (*Granulobacter bethesdensis*[49] and *Acidomonas methanolica*).[18,50]

A wide variety of opportunistic pathogens may lead to peripheral lymphadenitis in patients with human immunodeficiency virus (HIV) infection, particularly with progressive immunodeficiency. These include *H. capsulatum, Cryptococcus neoformans,*[43,51] *Pneumocystis jirovecii,*[52] and *Bartonella henselae*[53] (bacillary angiomatosis), as well as TB[54,55,56,57] and nontuberculous mycobacteria[58] and syphilis.[59] Parenchymal disease and lymphadenitis may coexist, although lymphadenitis may present in isolation. Lymphadenitis arising from mixed infections involving more than one of these opportunistic pathogens can occur (e.g., cryptococci and *Histoplasma*),[60] and specimens (either fine-needle samples or excisional biopsies) should be assessed thoroughly, both histologically and microbiologically, for precise diagnoses. Conversely, generalized or prominent regional lymphadenopathy may be present with progressive HIV infection in the absence of opportunistic infection and respond to antiretroviral therapy. Fine-needle aspiration cytology can be diagnostic of HIV lymphadenitis and occasionally establishes the diagnosis if prior serologic screening has not been performed.[61] Infectious lymphadenitis due to opportunistic pathogens may complicate advanced untreated HIV infection[51] or may flare after initial control of infection and subsequent initiation of highly active antiretroviral therapy as part of the immune reconstitution inflammatory syndrome.[62] Previously unrecognized latent or successfully treated infections may become prominent after immune reconstitution, and a thorough diagnostic evaluation, frequently requiring lymph node biopsy for microbiologic diagnosis and histopathology, is necessary. *M. tuberculosis*[63] or *Mycobacterium avium-intracellulare* lymphadenitis[64] as part of disseminated mycobacterial infection is a well-recognized complication of immune reconstitution inflammatory syndrome with important therapeutic and infection control implications, particularly in resource-limited settings.[56,57] Cryptococcal lymphadenitis developing after clinically successful primary therapy in the setting of subsequent immune reconstitution is also well known.[65,66,67] In addition, unusual microorganisms have been responsible for lymphadenitis on rare occasions in immunocompetent persons. Such microorganisms include *Rhodococcus equi, Y. pseudotuberculosis,*[68] *Corynebacterium pseudotuberculosis,*[69] nocardiosis,[70] and *Coxiella burnetii.*[71]

Specific Types of Nonpyogenic Regional Lymphadenitis

Scrofula (Tuberculous Cervical Lymphadenitis)

TB cervical adenitis, formerly a common disease in children and young adults, is now infrequent in modern societies but is still common in resource-limited settings.[72,73,74] It is still occasionally seen in individuals who immigrated to this country from endemic regions or in residents of rural areas in this country and reflects breakdown of previous cervical node TB, acquired by either ingestion of infected milk (bovine TB)[75] or lymphohematogenous spread of infection from an initial pulmonary focus to these lymph nodes. Cervical lymphadenitis due to *M. tuberculosis* is seen in this country in adults of particular ethnic groups: Native Americans, Latinos, and recent immigrants from Haiti and Asia. In the United States and other industrialized societies, tuberculous cervical lymphadenitis (scrofula) is now uncommon and is much more frequently due to atypical mycobacteria. Although *Mycobacterium scrofulaceum* was once the predominant pathogen in this setting, *M. avium-intracellulare* complex is now the principal etiologic agent[76,77,78,79] in children and adults. In recent years a number of newly recognized, difficult-to-isolate, and uncommon mycobacterial species have been reported as occasionally causing childhood cervical lymphadenitis, including *Mycobacterium interjectum, Mycobacterium malmoense, Mycobacterium haemophilum, Mycobacterium xenopi, Mycobacterium szulgai, Mycobacterium lentiflavum, Mycobacterium heidelbergense, Mycobacterium bohemicum,* and more than a dozen others, often requiring gene sequencing for definitive diagnosis.[78]

M. tuberculosis infections, including cervical lymphadenitis and other forms of extrapulmonary disease, are frequent in the HIV-infected population.[80] *M. tuberculosis* lymphadenitis in the HIV-infected patient differs in several respects from the infection in HIV-negative patients: a higher frequency of fever, common concomitant parenchymal infection, frequent negative purified protein derivative (PPD) skin tests (anergy), and a higher frequency of positive smears for acid-fast bacilli (and greater numbers of organisms) on fine-needle aspirates or excised lymph nodes.[81] Deep tuberculous lymphadenitis (e.g., lymphadenitis in relation to the bile duct) may occur and present with unusual features such as obstructive jaundice.[82]

In parts of the world where BCG vaccination of infants is commonly practiced, subcutaneous abscesses and regional lymphadenitis are not uncommon complications, occurring 2 to 8 weeks after vaccination but usually resolving spontaneously. On occasion, regional (axillary, supraclavicular, or cervical) lymphadenitis progressively enlarges and goes on to caseating suppuration.[20,21,83] This was once considered quite rare, but newer strains of BCG vaccine have been associated with markedly higher rates of suppurative adenitis (1/1543 cases), potentially limiting its use as a preventive measure.[84,85]

The onset of scrofula is insidious; fever and other systemic manifestations are present in only a small minority of cases. Several nodes are frequently enlarged and matted together, and the resultant mass may develop a swollen fluctuant area, which brings the patient to medical attention. The process is usually painless. In most cases clinical evidence of TB elsewhere is absent. Localized erythema may develop over the involved nodes and be followed by progressive fluctuance and spontaneous drainage of caseous material onto the skin surface (scrofuloderma).

Ultrasonography or CT may demonstrate deeper regional adenopathy in addition to the clinically apparent lymphadenitis. The identification of the mycobacterial species involved is important because management of mycobacterial lymphadenitis depends critically on whether the causative agent is *M. tuberculosis* or a nontuberculous mycobacterium. Excisional biopsy has the highest rates of microbiologic diagnosis (up to ≈90%), but in regions with high rates of endemic *M. tuberculosis* infection, fine-needle aspiration recovers *M. tuberculosis* in greater than 60% of cases[73] and is less invasive. *M. tuberculosis* lymphadenitis generally responds to conventional 6-month therapy with or without lymph node excision. Of interest, paradoxical reactions resembling the immune reconstitution syndrome have been observed in HIV-negative hosts receiving therapy for tuberculous lymphadenitis, with an initial favorable response followed by subsequent fever and apparent progression.[86]

Nontuberculous mycobacteria, most commonly *M. avium-intracellulare* complex, is responsible for the vast majority of cervicofacial mycobacterial lymphadenitis.[87] This is an uncommon process (annual incidence ≈1–5/100,000 children), which occurs predominantly in young, otherwise healthy children. Disease is usually unilateral and localized to submandibular or anterior cervical nodes. There is indolent progression over 1 to 3 months with nodal enlargement, followed by the development of overlying erythema, and in untreated cases, eventual sinus tract formation and drainage develops.

The nontuberculous mycobacteria causing cervical lymphadenitis, although often sensitive to macrolide agents, are frequently largely resistant to conventional antituberculous chemotherapy, and surgical excision of the involved fluctuant node or nodes is indicated,[88–91] both for initial control of infection and for recovery of the pathogen for drug susceptibility testing. Adjunctive therapy with rifampin and clarithromycin is sometimes considered when treating *M. avium-intracellulare* lymphadenitis in normal hosts, especially when imaging by ultrasonography or CT demonstrates extensive deep lymph node involvement or involvement of submandibular nodes abutting the facial nerve, which precludes total excision. Multidrug therapy is required to treat these infections in compromised hosts, such as HIV patients in whom bacillemia is common and the infection is best considered a systemic illness requiring prolonged systemic therapy. Antituberculous therapy is usually not necessary for BCG nonsuppurative lymphadenitis, but if suppurative lymphadenitis develops, aspiration[83] or complete excision and multidrug antituberculous chemotherapy are indicated.[20]

Granulomatous Lymphadenitis Caused by Nondiphtheria Corynebacteria

Subacute or chronic relapsing lymphadenitis has been reported occasionally to be due to *Corynebacterium pseudotuberculosis (Corynebacterium ovis).* Most patients have lived in Australia[92] and have had extensive contact with animals, particularly sheep, in which *C. pseudotuberculosis* is a common cause of caseous lymphadenitis. The histologic picture is that of a suppurative or necrotizing granulomatous process. Treatment consists of prolonged antibiotic (erythromycin or penicillin) therapy combined with surgical drainage or excision of the involved nodes.

Oculoglandular (Parinaud) Syndrome

Preauricular lymphadenopathy can occur secondary to granulomatous nodular conjunctival infection caused by the introduction of certain pathogens to the external eye. Oculoglandular syndromes occur occasionally in tularemia, cat-scratch disease,[93,94] listeriosis, sporotrichosis, adenovirus infection, murine typhus,[95] and LGV. Epidemic keratoconjunctivitis due to adenoviruses is often associated with an enlarged preauricular lymph node as well.

Cat-Scratch Disease

Cat-scratch disease[93,96] is a slowly progressive and sometimes chronic form of regional lymphadenitis caused by *B. henselae* (see Chapter 234). Although cat-scratch disease is usually a benign and ultimately self-limited process, it may be complicated by acute encephalitis, hepatitis, osteomyelitis, neuroretinitis, arthritis, pleuritis, atypical pneumonia, hilar adenopathy, and thrombocytopenia.[96] *B. henselae* bacilli are slow growing, requiring 2 to 6 weeks of incubation in a moist environment (e.g., in a sealed gas-permeable plastic bag) under 5% carbon dioxide for growth on blood-agar plates (human blood is preferable to sheep or horse blood).

Approximately 90% of patients with cat-scratch disease give a history of contact with cats (most often kittens), and most have been scratched. A primary lesion (small papule or vesicle resembling an insect bite) develops at the site of the scratch 7 to 14 days after contact with the animal. This primary lesion lasts for several weeks to months and may be helpful in diagnosis, but it is not always present when the patient presents for evaluation. Lymphadenopathy develops within 1 to 3 weeks of the appearance of the skin papule.[96] There is no lymphangitis. The lymphadenopathy progresses to suppuration in 10% to 50% of cases, but the course is slower than that of suppurative lymphadenitis due to pyogenic bacteria, and most patients are only mildly ill. Regional lymphadenitis is the sole manifestation of cat-scratch disease in half of the cases. Individuals receiving anti–tumor necrosis therapies have been reported to experience stereotypic cat-scratch adenitis and not

disseminated bartonellosis.[97] Almost any peripheral lymph node may be involved, including isolated involvement of epitrochlear or mediastinal nodes, but the axillary nodes are most commonly affected. The nodes are tender, especially when there is frank suppuration. Low-grade fever is present in only a third of patients. Approximately 10% to 15% of patients have features of a more systemic illness: anorexia, headache, weight loss, and hepatosplenomegaly. Unusual clinical presentations include Parinaud oculoglandular syndrome (conjunctivitis from ocular inoculation associated with ipsilateral preauricular lymphadenopathy) in 4% of patients,[94] neuroretinitis, and, rarely, acute encephalitis/encephalopathy, usually with a sudden seizure as the initial neurologic manifestation, occurring several weeks after the first symptoms of cat-scratch disease. *B. henselae* infection has been confirmed by polymerase chain reaction (PCR) testing of biopsy tissue[98] within the first 6 weeks of lymphadenopathy and from conjunctival scraping in the setting of Parinaud oculoglandular syndrome.[93] Chronic generalized lymphadenopathy due to *Bartonella henselae* has been observed in HIV-infected patients in the absence of bacillary angiomatosis.[99] *B. henselae* infections can be confirmed serologically at the Centers for Disease Control and Prevention and other reference laboratories.

Mediastinal Lymphadenopathy

In contrast to acute or subacute peripheral regional lymphadenitis in which local signs and symptoms prompt medical attention, mediastinal lymphadenitis is sometimes detected only in the course of evaluation of nonlocalizing systemic symptoms, such as fever and weight loss, or primarily pulmonary symptoms, such as cough, chest pain, and sputum production. Distinctive radiologic features may support particular diagnoses. Symmetrical hilar adenopathy with clear lung fields or symmetrical interstitial fibrosis suggests sarcoidosis, particularly when accompanied by any of a variety of extrathoracic manifestations. Asymmetrical or unilateral hilar adenopathy, particularly when associated with ipsilateral chronic focal lung disease with calcification, fibrosis, and/or cavitation, suggests TB or fungal infection. Peripheral rim enhancement of mediastinal lymph nodes on contrast-enhanced CT imaging is characteristic of granulomatous lymphadenitis and implicates TB, histoplasmosis, or cryptococcosis.[100] The presence of mediastinal widening in association with subacute or chronic mediastinal lymphadenopathy strongly suggests histoplasmosis. *Cryptococcus* can cause mediastinal lymphadenitis or mediastinitis, or both, in immunocompromised hosts, mimicking lymphoma,[101] and in HIV patients as part of acquired immunodeficiency syndrome (AIDS), particularly in the immune reconstitution syndrome. Mediastinal lymphadenitis in organ transplant recipients may be caused by a variety of expected and unusual pathogens, including *Rhodococcus*.[102] The underlying health, travel and exposure history, extrapulmonary signs and symptoms, and ancillary laboratory tests (e.g., angiotensin-converting enzyme levels, anergy) may all contribute to a presumptive diagnosis. Ultimately most adults require lymph node biopsy or transbronchial lung biopsy for pathologic and microbiologic confirmation to address possible infection by uncommon pathogens or nodal involvement by noninfectious causes,[103] such as sarcoidosis,[104] inhalational disorders such as silicosis and berylliosis, drug reactions (e.g., phenytoin), primary amyloidosis, Kikuchi-Fujimoto disease,[105] Castleman disease, or malignancy. Necrotic, edematous hilar and mediastinal lymph nodes are early events in inhalation anthrax (see Chapter 207).

Inguinal Buboes of Sexually Transmitted Disease

Inguinal lymphadenopathy due to pyogenic infections or cat-scratch disease is usually unilateral. Prominent bilateral (or unilateral) adenopathy, particularly in men, is suggestive of several sexually transmitted diseases. The genital chancre of primary syphilis is usually accompanied by one or several discrete, firm, nonsuppurative, painless, enlarged nodes in one or both inguinal areas. Constitutional signs are lacking. The overlying skin is uninflamed. In secondary syphilis painless generalized lymphadenopathy usually precedes the characteristic cutaneous eruption.

LGV infections arise after the sexual transmission of selected *Chlamydia trachomatis* serovars. The asymptomatic primary genital lesion (painless papule, vesicle, or erosion) is usually transient. The initial manifestation of the disease after heterosexual transmission is usually the characteristic inguinal bubo, occurring 10 to 30 days after sexual exposure and 1 to 2 weeks after the primary lesion. The adenopathy is more commonly unilateral. Initially the node is tender, discrete, hard, and movable, but subsequently the inflammatory process involves multiple nodes in the area. Chills, fever, and constitutional symptoms are common at this stage. As a result of periadenitis, the nodes become fixed and matted into an oval or lobulated mass. The mass is adherent to the overlying skin, which is purplish. Foci of suppuration develop, with multiple fistulous tracts. A central lengthwise linear depression (so-called groove sign of LGV) is produced by involvement of nodes above and below the inguinal ligament. Although characteristic of LGV, the groove sign may rarely be produced by suppurative bacterial lymphadenitis or lymphomatous involvement of inguinal nodes. In the past decade there has been an epidemic of LGV in industrialized nations involving men who have sex with men; although proctitis and proctocolitis have been the dominant clinical features,[106] inguinal lymphadenitis has been present in approximately 10% of cases.[107] The diagnosis can be made serologically and clinically after a satisfactory response to doxycycline therapy.[108] Culture and molecular methods of diagnosis (e.g., PCR) are available in reference laboratories.[108]

Chancroid is usually accompanied by painful, tender, inguinal adenopathy. The primary lesion is a papule or pustule that progresses to form an extremely painful and tender but nonindurated ulceration with undermined edges, quite in contrast to a syphilitic chancre. Autoinoculation is common, with lesions on opposing or contiguous areas of the skin. The adenopathy of chancroid develops approximately 1 to 2 weeks after the primary lesion appears and, unlike in LGV, is present while the ulcer is still active. Systemic symptoms accompany chancroid only rarely. The chancroidal bubo is typically unilateral and composed of fused inguinal nodes and is more painful than that of LGV. Unilocular suppuration may develop, although in most patients the lymphadenitis subsides without suppuration. As with a variety of pathogens, individuals dually infected with HIV and *Haemophilus ducreyi* have more severe and extensive ulceroglandular disease.[109] A nonsexual form of *H. ducreyi* infection associated with chronic leg ulcers has been recognized in the Pacific region and in Africa.[110]

Primary genital herpes simplex infection in men and women is often associated with tender inguinal adenopathy, with evidence of focal necrosis, viral intranuclear cytopathic effects, and giant cell formation if involved lymph nodes are subjected to biopsy. Similar histologically proven, recurrent, localized and generalized herpetic lymphadenitis can occur in immunocompromised patients in the absence of overt mucocutaneous lesions.[5,111] The pseudobuboes of granuloma inguinale are produced by subcutaneous granulomatous infection rather than by suppurative lymphadenitis.

Inguinal Buboes of Other Than Sexually Transmitted Disease Origin

Inguinal or femoral buboes occur in bubonic plague because the flea bite initiating the infection is commonly on a lower extremity,[112] but involvement of other peripheral nodes can occur. The disease begins with fever, malaise, headache, and tender regional adenopathy after an incubation period of 2 to 6 days. Only rarely is a lesion (papule, pustule) at the insect bite site evident at the onset of illness. A large, matted collection of lymph nodes with surrounding edema quickly develops and may go on to suppuration and spontaneous drainage. If not treated promptly, the infection rapidly progresses to a septicemic or pneumonic phase. The diagnosis should be suspected in a febrile, acutely ill patient with a large cluster of extremely tender lymph nodes and a history of exposure to fleas, rodents, or rabbits in the western United States[113] (see Chapter 229). One must consider possible plague when hunters, backpackers, or rural workers from this region develop a compatible illness, even in the absence of definite exposures to these vectors. Tularemia may mimic the epidemiologic and clinical features of bubonic plague but is more likely to produce an ulceroglandular or pure glandular syndrome[114] (Table 95.1), with a primary lesion at the site of inoculation.[115] Cutaneous anthrax is another cause of ulceroglandular infection, but the marked local edema and eschar formation at the site of inoculation dominate the clinical picture.[26] Diagnostic procedures include blood

TABLE 95.1 Forms of Lymphadenitis

DISEASE	INFECTING ORGANISM	REGIONAL	REGIONAL WITH SUPPURATION (OR CASEATION)	INGUINAL BUBO FORMATION	ULCEROGLANDULAR	OCULOGLANDULAR	GENERAL
Bacterial							
Pyogenic	Group A or B streptococci, *Staphylococcus aureus*	+	+				
Scarlet fever	Group A streptococci	+	+				+
Diphtheria	*Corynebacterium diphtheriae*	+					
Fusospirochetal angina	*Prevotella melaninogenica*, peptostreptococci, etc.	+					
Scrofula	*Mycobacterium tuberculosis* *Mycobacterium scrofulaceum* *Mycobacterium avium-intracellulare*	+ + +	+ + +				
Miliary tuberculosis	*M. tuberculosis*	+					+
Brucellosis	*Brucella*	+					+
Leptospirosis	*Leptospira*	+					+
Syphilis	*Treponema pallidum*	+					+
Chancroid	*Haemophilus ducreyi*	+					
Plague	*Yersinia pestis*	+	+	+			
Tularemia	*Francisella tularensis*	+	+	+	+	+	
Rat-bite fever	*Streptobacillus moniliformis* *Spirillum minus*	+ +			+ +		
Anthrax	*Bacillus anthracis*	+	+		+		
Listeriosis	*Listeria monocytogenes*	+					
Melioidosis	*Burkholderia pseudomallei*	+	+	+			
Glanders	*Burkholderia mallei*	+	+	+			
Cat-scratch disease	*Bartonella henselae*	+	+	±	±	+	
Typhoid fever	*Salmonella typhi*	+					
Mycotic							
Histoplasmosis	*Histoplasma capsulatum* *H. capsulatum* var. *duboisii*	+ +					
Coccidioidomycosis	*Coccidioides immitis*	+					
Paracoccidioidomycosis	*Paracoccidioides brasiliensis*	+					
Cryptococcosis	*Cryptococcus neoformans*	+	+				
Rickettsiae							
Boutonneuse fever, etc.	*Rickettsia conorii*	+					
Scrub typhus	*Rickettsia tsutsugamushi*	+					
Rickettsialpox	*Rickettsia akari*	+					
Chlamydial							
Lymphogranuloma venereum	*Chlamydia trachomatis*	+	+	+			