Myositis, Pyomyositis, and Necrotizing Fasciitis

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Skin and soft-tissue infections (SSTIs) are common in children and usually are recognized easily and treated, with few residual long-term problems. However, although rare, myositis, pyomyositis, and necrotizing fasciitis soft-tissue infections can be difficult to diagnose in their early stages and despite appropriate antibiotic therapy are associated with substantial morbidity and mortality. The epidemiology of SSTIs is evolving, and incidence in children is increasing. Community-associated methicillin-resistant S. aureus (CA-MRSA) first emerged among children in the 1990s. Since then CA-MRSA has become the predominant cause of purulent SSTIs in the United States. Coincident with this epidemic, the incidence of pediatric ambulatory visits for SSTIs has nearly tripled.1 Also in immunocompromised children SSTIs can be atypical and/or more severe.2

MYOSITIS

Myositis is defined as inflammation of a muscle, especially a voluntary muscle, characterized by pain, tenderness, swelling, and/or weakness. Etiologies of myositis include infection, autoimmune conditions, genetic disorders, medications, electrolyte disturbances, and diseases of the endocrine system.3 Infectious myositis can be due to bacteria, fungi, parasites, and viruses (Table 77-1).3 The clinical course can be acute, subacute, or chronic. Although identification of the causative microbe requires specific diagnostic testing (e.g., cultures), some clinical findings suggest the general category of the agent. For example, bacterial myositis usually causes focal muscle infection, whereas viruses and parasites often cause generalized myalgias or multifocal myositis. Also, bacterial myositis often occurs in the setting of muscular injury, surgery, ischemia, or the presence of a foreign body.

Bacterial Myositis

Acute bacterial myositis, defined as a diffuse muscle infection without an intramuscular abscess, occurs less commonly than pyomyositis and psoas abscess formation. Myositis compared with pyomyositis is seen more typically in adults rather than children.

Staphylococcus aureus. Although S. aureus myositis is uncommon, incidence has increased in adults and children in recent years, largely due to the emergence of CA-MRSA.4,5 In the U.S., the USA300 clone of CA-MRSA accounts for most infections. It appears that virulence has evolved in this strain through the increased expression of core-genome-encoded virulence determinants, such as α-toxin and phenol-soluble modulins, and acquisition of the phage-encoded Panton–Valentine leukocidin (PVL) genes. All these toxins impact disease progression in animal models of USA300 infection. In contrast, the basis of virulence in other CA-MRSA epidemics, which include PVL-negative strains, is less well understood.5–7

Streptococcus pyogenes. S. pyogenes (group A streptococci; GAS) also can cause myositis. The most severe form is necrotizing myositis, also called streptococcal myonecrosis or spontaneous streptococcal gangrenous myositis. Cases typically occur among men (2 : 1) and young adults; the disease usually occurs spontaneously without a history of penetrating trauma or underlying immunosuppression. The portal of entry often is unknown. Some cases begin with a sore throat, suggesting that pharyngitis may have led to bacteremia and seeding of the muscle; however, most cases occur without an antecedent illness. The clinical presentation includes an initial prodromal stage with flu-like symptoms, which may include rash and myalgias. This evolves to intense local...
TABLE 77-1. Common Infectious Causes of Myositis*

<table>
<thead>
<tr>
<th>Organism Group</th>
<th>Organism(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram-positive bacteria</td>
<td>Staphylococcus aureus, Streptococcus pyogenes (group A streptococcus), Streptococcus (groups B, C, and G, S. pneumoniae, S. arginosus)</td>
</tr>
<tr>
<td>Anaerobic bacteria</td>
<td>Bacteroides spp., Clostridium spp., Streptococcus spp. (anaerobic, e.g., Peptostreptococcus)</td>
</tr>
<tr>
<td>Mycobacterium spp.</td>
<td>Mycobacterium tuberculosis</td>
</tr>
<tr>
<td>Fungi</td>
<td>Candida spp.</td>
</tr>
<tr>
<td>Parasites</td>
<td>Trichipleistophora, Plasmodium spp., Sarcocystis spp., Taenia solium, Trichinella spp.</td>
</tr>
<tr>
<td>Viruses</td>
<td>Enteroviruses (coxsackie B virus and ECHO virus), HIV, HTLV-1, Influenza A and B viruses</td>
</tr>
</tbody>
</table>

*Modified from reference 3.

muscle pain that is disproportionate to clinical findings as well as local tense swelling and fever. The course can evolve rapidly over several hours (Figure 77-1). **Clostridium species.** Clostridial gas gangrene (i.e., myonecrosis) most commonly is caused by *C. perfringens, C. novyi, C. histolyticum,* and *C. septicum.* *C. perfringens* is the most frequent cause of trauma-associated gas gangrene. This infection occurs in a variety of settings: traumatic wounds with soil contamination, surgery involving the bowel or biliary system, septicaemia, vascular disease with arterial insufficiency, and in association with injection of medications (e.g., epinephrine) or illicit drugs (e.g., heroin). Common characteristics of inciting events include contamination of the site with *Clostridium* spp. (which exist in the soil and as part of the gastrointestinal flora of humans) and the presence of devitalized tissue. The presence of a foreign body is a risk factor. In contrast to traumatic gas gangrene, spontaneous gangrene principally is associated with the more aerotolerant *C. septicum* and occurs predominantly in patients with underlying gastrointestinal conditions, including occult colon cancer, bowel infarction, or neutropenic enterocolitis.

*C. septicum* infections occur in children in three major predispositions: neutrophil dysfunction (including malignancies, congenital or cyclic neutropenia, aplastic anemia), bowel ischemia (hemolytic-uremic syndrome, intussusception), and trauma. Malignancy underlies >50% of cases, with acute myelocytic and lymphocytic leukemias the most common. Cyclic and congenital neutropenia is present in 20% of the published pediatric cases. Clinical features associated with *C. septicum* infections in children include fever, vomiting, diarrhea, blood per rectum, anorexia, and acute abdomen and/or distention. Despite treatment with surgery and parenteral antibiotics, mortality rates of children with *C. septicum* infections remain >50%.**

Presenting symptoms for clostridial myonecrosis include intense pain, edema, and a sweet-odorous discharge which occur several hours to a few days after injury. The wound initially is pale but can evolve to a bronze color with hemorrhagic bullae. Classic findings include the presence of gas in the tissues detected by either gas bubbles emitted from the wound or noted on radiographic films. Although gas often is considered to be a sine qua non for gas gangrene, the absence of crepitus or gas on examination should not deter consideration of this diagnosis. The failure of the muscle to contract on stimulation and the lack of bleeding of the wound during operation are characteristic findings. Typical laboratory findings include leukocytosis and a hemolytic anemia due to clostridial $\alpha$-toxin. Bacteremia is noted in 15% of cases. Gram stain evaluation of the wound exudate usually shows a lack of neutrophils and an abundance of gram-positive bacilli with blunt ends.

**Nonclostridial myositis.** Anaerobic streptococcal myositis has similar clinical characteristics of clostridial myonecrosis, including a foul copious exudate, gas in infected tissues, and extensive necrosis of the involved muscle(s). Specific etiologies include anaerobic streptococci (e.g., *Peptostreptococcus* spp.), GAS, and *S. aureus.* Synergistic nonclostridial myonecrosis is an infection of the subcutaneous tissues and fascia that can extend into the muscle. The infection often is polymicrobial, consisting of aerobic and anaerobic organisms, such as streptococci (including *Peptostreptococcus* spp.), *Bacteroides* spp., *E. coli,* Enterobacter spp., and *Klebsiella* spp. *Aeromonas hydrophila* myonecrosis usually occurs after penetrating trauma in a freshwater environment or tissue injury in association with contact with aquatic animals. Progression can be rapid and gas may form within the tissues.

*Vibrio vulnificus* is an opportunistic human pathogen that is highly lethal. The bacterium is a part of the natural flora of coastal marine environments worldwide and has been isolated from water, sediments, and a variety of seafood. Of all *Vibrio* infections reported in the U.S. annually, 25% to 30% are non-foodborne *Vibrio* infections (NVFIs). *V. vulnificus* infections are the most common (accounting for 35% of NVFIs), with 72% of *V. vulnificus* infections occurring in children with acute onset of fever, erythema, swelling, and pain of her right shoulder, and decreased use of her arm. There was no break in the skin. Coronal fluid-attenuated inversion recovery (FLAIR) magnetic resonance imaging shows diffuse hyperintensity of the deltoid muscle with associated subcutaneous inflammatory stranding and edema. Osseous and fascial structures are normal. (Courtesy of E.N. Faerber and S.S. Long, St. Christopher’s Hospital for Children, Philadelphia, PA.)
Infections reported from residents of Gulf Coast states. SSTIs due to \textit{V. vulnificus} result in amputation and death in 10% and 17% of cases, respectively. \textsuperscript{11} Clinicians should consider \textit{Vibrio} species as an etiologic agent in infections occurring in persons with recent seawater exposure, even if the individual was only exposed during recreational activities.

**Other forms of bacterial myositis.** Lyme disease can cause localized myositis of the orbits and other sites, often near areas of erythema migrans or joint involvement. \textsuperscript{12} Mycobacterium spp. causes myositis either by direct extension from a contiguous source (e.g., an infected joint, bone, or abscess) or less commonly via bacteremia. The most common site is a tuberculous psosas muscle abscess that forms by extension from vertebral osteomyelitis (i.e., Pott disease). Other examples include involvement of the intercostal muscles through extension from the lung or striated muscles of the leg through extension from the knee.

**Fungal Myositis**

Fungal myositis is uncommon with most cases occurring in immunocompromised patients. Fungal myositis can be due to \textit{Candida} spp. (most commonly), \textit{Cryptococcus neoformans}, \textit{Histoplasma capsulatum}, \textit{Coccidioides} spp., \textit{Aspergillus} spp., \textit{Pneumocystis jirovecii}, and \textit{ Fusarium} spp. Biopsy with culture usually is required to confirm the diagnosis. Often the diagnosis is not considered initially and is discovered by histopathology or culture of muscle tissue.

**Parasitic Myositis**

A variety of parasites can encyst in muscle. The most common are \textit{Trichinella} spp. (trichinosis), \textit{Toxocara canis} (cytocercosis), and \textit{Toxoplasma gondii} (toxoplasmosis). The presence of eosinophilia and a travel history to an endemic area suggest a possible parasitic etiology of myositis.

Infection with \textit{Trichinella spiralis} occurs after ingestion of larval cysts in undercooked pork or the meat of certain wild carnivores. The adult worm develops in the gastrointestinal tract and releases larvae that circulate via lymphatics and the bloodstream to striated muscle, where they become encysted and survive for several years. The vast majority of infections are subclinical; autopsies reveal \textit{Trichinella} cysts in >4% of randomly selected diaphragms. \textsuperscript{13} Typical manifestations of symptomatic disease include fever, extreme malaise, muscle pain, weakness, and periorbital edema. \textsuperscript{14} Serum muscle enzymes are elevated, and eosinophilia is present. Serodiagnostic testing is available and can preclude the need for biopsy. Most mild cases respond to analgesic therapy. In severe cases, anesthetic therapy with thiabendazole or mebendazole is effective. \textsuperscript{15}

After ingestion of eggs of the pork tapeworm \textit{Taenia solium} larvae migrate to extracranial skeletal muscle leading to granulomatous nodules and calcific densities. Although fever, myalgia, and eosinophilia can occur, most cases of muscular cytosis, except those involving extracranial muscles, are asymptomatic. For infections that involve extracranial muscles, treatment with albendazole plus a corticosteroid or surgical removal of the encysted parasites may be necessary to preserve vision. \textsuperscript{16}–\textsuperscript{18} During acute \textit{Toxoplasma gondii} infection, widespread dissemination of tachyzoites can occur, and skeletal muscle frequently is infected. The vast majority of cases of acquired toxoplasmosis are asymptomatic, although some patients experience a mononucleosis-like syndrome with nonspecific myalgia. Chronic inflammatory myositis associated with \textit{T. gondii} has been reported in human immunodeficiency virus (HIV-1)-infected and other immunocompromised people. \textsuperscript{19} Weakness, muscle wasting, and high serum levels of creatine kinase are characteristic features. Infection in the acute phase may be responsive to pyrimethamine plus sulfadiazine, whereas in the chronic phase, corticosteroid therapy may be beneficial. \textsuperscript{20}

**Viral Myositis**

Many viruses can cause myalgias, polymyositis, or virus-associated rhabdomyolysis. Often the symptoms of myositis are diffuse in nature, and patients have other symptoms and signs attributable to the causative viral pathogen. Influenza A and B viruses are the most commonly reported causes of viral myositis. Enteroviruses, HIV, human T-cell leukemia-lymphoma virus (HTLV-1), and hepatitis viruses (B and C) also can cause myositis.

Influenza-associated myositis (IAM) has been reported only sporadically since its first description in 1957. IAM appears to be more common in children than in adults, but its age-specific prevalence during influenza epidemics is unknown. \textsuperscript{21} IAM is characterized in children by severe lower-extremity myalgia and reluctance to walk. As IAM is associated with the influenza B virus, incidence may depend on circulating strains during an epidemic. IAM typically occurs with a 2 : 1 male predominance among children aged <14 years and is characterized by abrupt onset of severe myalgia in calf muscles, inability to walk, and elevated serum creatine kinase levels, usually within 1 week of influenza onset, when respiratory symptoms are improving. Whereas the link between influenza and IAM is clearly established, its pathogenesis is not well understood. Two proposed mechanisms are viral invasion of muscle tissue and immune-mediated muscle damage triggered by the respiratory tract infection. Treatment is symptomatic, as myositis is self-limited, usually resolving within a mean of 3 days (range, 1 to 30 days). Influenza virus-associated rhabdomyolysis has been described in children and adults. Rhabdomyolysis is associated more frequently with influenza type A than type B, and occurs more frequently in girls. The 2009 pandemic triple-reassortant influenza A (H1N1) virus was associated with neurologic and muscular syndromes that affected primarily children and included myositis. \textsuperscript{22} Rhabdomyolysis can be complicated by renal failure and the development of a compartment syndrome.

Enteroviruses, including coxsackieviruses (group A and B) and enteric cytopathogenic human orphan (ECHO) viruses, also cause myositis. Coxsackievirus B infection manifesting as pleurodynia is most common. Typically children come to attention in the summer or fall with paroxysms of severe, sharp chest pain. The costochondral muscles may be tender on palpation. In addition to pleurodynia, cases of rhabdomyolysis due to coxsackieviruses and ECHO viruses have been reported. The pathogenesis of myositis is uncertain, but muscle biopsies have shown degenerative necrosis of the muscle fibers and picornavirus-like structures. Therapy is symptomatic; the disease usually resolves in several days, but recurrences of pleurodynia have been described in up to one-fourth of cases.

HIV infection can cause a wide range of skeletal disorders including myopathy, polymyositis, and rhabdomyolysis. Generalized myalgia, proximal muscle weakness, and elevated serum creatine kinase are frequent features. \textsuperscript{23} Muscle biopsy shows lymphocytic infiltration and necrosis of muscle fibers. These histologic findings are distinct from the mitochondrial myopathy associated with extended zidovudine therapy. \textsuperscript{24} Although one study has shown that proviral DNA can be detected in myocytes and muscle macrophages by polymerase chain reaction, \textsuperscript{25} other researchers have concluded that the disease probably represents a dysfunctional T-lymphocyte-mediated process. \textsuperscript{26} Corticosteroid therapy may be beneficial. \textsuperscript{27}

**Chronic Inflammatory Myositis**

A number of parasitic and other pathogens can cause a chronic inflammatory reaction in skeletal muscle. In these disorders, persistence of the infectious agent appears necessary to cause chronic myopathy, either by direct tissue damage or as a consequence of the normal immuneologic response directed toward the infected tissue. In other disorders, such as juvenile dermatomyositis (JDM) and polymyositis, an immunologic dysregulation is the hypothesized mechanism of disease. \textsuperscript{28} JDM is the most common form of pediatric idiopathic inflammatory myopathy, with incidence ranging from 1.9 to 3.2 per million children. \textsuperscript{29,30} The two major clinical features of JDM are a characteristic rash and symmetric proximal muscle weakness. \textsuperscript{31} The gastrointestinal tract and lung also often are involved. \textsuperscript{32}
Compared with the adult form of the disease, JDM more frequently has vasculitis features, skin ulceration, and calcinosis. Patients with JDM often experience a flu-like illness approximately 3 months prior to the onset of the disease. Coxsackievirus B and other enteroviruses are the most frequent infectious agents temporally associated with the onset of JDM. Coxsackievirus B1 can induce chronic myositis of the proximal hindlimbs in a murine model. Serologic responses consistent with acute coxsackievirus B infection were found in patients in some studies but not in others. Although picornavirus-like particles have been observed on electron-microscopic examination of muscle biopsy samples from some children with JDM, immunofluorescence, polymerase chain reaction, in situ nucleotide hybridization, and tissue culture have failed to identify a virus. If an infectious agent precipitates JDM, it is hypothesized that immunologically mediated injury (possibly through molecular mimicry), rather than direct infection, is the mechanism of injury. This pathogenic mechanism is supported by gene expression profile analyses of untreated JDM muscle biopsies, demonstrating an intense interferon α/β-induced response typical of that seen during an immune response to a viral antigen.

Several reports have demonstrated an association between the human leukocyte antigen (HLA)-DQA1*0501 and JDM. This association has been linked to an enhanced cytokine response partly contributed to by the tumor necrosis factor-alpha (TNF-α)-308A allele, which is known to promote TNF-α synthesis. Enhanced TNF-α production was demonstrable in both circulation and in muscle biopsies from untreated JDM patients positive for the TNF-α-308A allele. This allele has been shown to be associated with pathologic calcifications and disease chronicity. The pathogenesis of JDM following group A streptococcal infection has been suggested to involve cytotoxic and cytokine responses elicited by specific epitopes of the streptococcal M-protein homologues of human skeletal myosin.

**PYOMYOSITIS**

Pyomyositis is an acute intramuscular infection secondary to hematogenous spread of the microorganism into the body of a skeletal muscle. By definition, it is not secondary to a contiguous infection of the soft tissue or bone, nor due to penetrating trauma. Pyomyositis has a predilection for large-muscle groups and often results in localized abscess formation. Pyomyositis often is called tropical myositis because of its prevalence in tropical areas, where pyomyositis accounts for 3% to 5% of hospital admissions. The first case of tropical pyomyositis reported from a temperate region was in 1971. Since then many cases have been reported from various parts of the world. Within North America, the highest incidence of pyomyositis is in southern regions. Pyomyositis occurs most often in children and young adults. It exhibits a 2:1 male preponderance, and has been reported in the neonatal period. Methicillin-susceptible S. aureus (MSSA) was isolated from the purulent material in approximately 90% of cases in tropical areas and 75% of cases from temperate countries prior to the 1990s. CA-MRSA (especially the USA300 clone) has since emerged as an important/dominant cause in temperate climates. Group A streptococci account for 1% to 5% of cases. Other causes include streptococci (group B, C, and G), E. coli, Citrobacter freundii, Serratia marcescens, Versinia enterocolitica, Klebsiella spp., and Salmonella spp. Individuals infected with HIV-1 are at increased risk for development of bacterial pyomyositis, sometimes with multifocal involvement.

Staphylococcal pyomyositis most frequently affects the quadriceps, hamstring, or gluteal muscles but also can affect the paraspinus, shoulder girdle, psosas, and other muscles. Symptoms generally begin insidiously, with low-grade fever, muscle aches, and cramping evolving over several days. Antibiotics and surgery are often ineffective in about 25% of patients. In the early stages, examination may reveal only a hard, rubbery firmness to the muscle belly, with no other superficial signs of inflammation. Within days to 3 weeks, boggy swelling, erythema, tenderness, and warmth appear, and the lesion becomes fluctuant. Although substantial muscle destruction can develop with delayed treatment, serum levels of muscle enzymes generally are normal. Pyomyositis occasionally is complicated by metastatic infection such as empyema, periartitis, or lung abscess. In rare cases, fulminant septicemia or toxic shock syndrome occurs.

Pyogenic abscess in the psosas muscle produces a distinct clinical syndrome with lower abdominal or back pain radiating to the hip. The febrile child may limp or hold the hip in fixed flexion because of muscle spasm. Confusion with pyogenic arthritis is common. Pain on hyperextension or abdication of the hip is elicited on examination. S. aureus is the most common cause, but psosas abscess occasionally can develop as an extension of an abdominal process such as a ruptured appendix. In such cases, a mixed infection with anaerobic and facultative bowel flora is likely.

Group A streptococci are an increasingly important cause of pyomyositis. GAS infection of skeletal muscle can present as an localized phlegmon, an abscess, or more fulminant necrotizing myositis. Intense pain is the most common presenting symptom, often out of proportion to clinical signs of inflammation. The child may refuse to bear weight or to move an extremity. Ultimately, high fever, localized swelling, and overlying erythema are observed. Tachycardia, hypotension, oliguria, confusion, leukocytosis with immature neutrophils (often more than 50%) and elevation of blood urea nitrogen, creatinine, and creatine kinase are common.

Although a portal of entry is not always evident, the exanthem of primary varicella and various forms of minor skin trauma are important predisposing factors to the development of GAS deep-tissue infection in children. A prospective population-based active surveillance for pediatric invasive GAS disease in Ontario revealed that varicella-zoster virus infection is associated with a 58-fold increased risk of invasive GAS disease in children. Although the attack rate of invasive GAS was relatively low (5.2/100,000), 15% of all pediatric invasive GAS infections, including 50% of cases of necrotizing fasciitis, followed varicella infection.

**NECROTIZING FASCIITIS**

Necrotizing fasciitis (also known as hospital gangrene or hemoletic streptococcal gangrene) was described as early as the fifth century BC by Hippocrates. Necrotizing fasciitis is a rapidly progressive, deep-seated bacterial infection of the subcutaneous soft tissue that can involve any area of the body. The course often is fulminant and has a high mortality rate, ranging from 25% to 75%. Many terms have been used to describe necrotizing soft-tissue infections. A simplified classification is provided in Table 77-2.

Although more than 500 cases of necrotizing fasciitis have been reported in North America, it is an uncommon disease and the true incidence is not known. Males are affected slightly more commonly than females. An increased frequency is associated with diabetes mellitus, intravenous drug use, chronic alcohol consumption, immunosuppression, and peripheral vascular disease. Necrotizing fasciitis also occurs in young, previously healthy children and adults, in whom mortality rates are lower than among the elderly and those with underlying disease. Patients may report a history of recent surgery, trauma, eczema, or varicella infection. Other precipitating factors include insect bites, perirectal abscess, incarcerated hernia, and subcutaneous insulin injection. Necrotizing fasciitis commonly is reported as a complication of varicella infection. Necrotizing fasciitis can also occur with a preceding GAS pharyngitis or without any previous evidence of trauma or infection. The association between the use of corticosteroids and necrotizing fasciitis was not supported definitively by a prospective, multicenter case-control study carried out among children hospitalized with primary varicella complicated by invasive GAS infection or necrotizing soft-tissue infection. In neonates, necrotizing fasciitis can complicate omphalitis or circumcision.
TABLE 77-2. Necrotizing Infections of the Soft Tissues

<table>
<thead>
<tr>
<th>Type</th>
<th>Usual Etiologic Agent</th>
<th>Predisposing Causes</th>
<th>Clinical Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meleney synergistic gangrene</td>
<td><em>Staphylococcus aureus</em>, microaerophilic streptococci</td>
<td>Surgery</td>
<td>Slowly expanding ulceration confined to superficial fascia</td>
</tr>
<tr>
<td>Clostridial cellulitis</td>
<td><em>Clostridium perfringens</em></td>
<td>Local trauma or surgery</td>
<td>Gas in skin, fascial sparing, little systemic toxicity</td>
</tr>
<tr>
<td>Nonclostridial anaerobic cellulitis</td>
<td>Mixed aerobes and anaerobes</td>
<td>Diabetes mellitus</td>
<td>Gas in tissues</td>
</tr>
<tr>
<td>Gas gangrene</td>
<td>Clostridial species (<em>Clostridium perfringens</em>, <em>Clostridium histolyticum</em>, or <em>Clostridium septicum</em>)</td>
<td>Trauma, crush injuries, epinephrine injections; spontaneous cases related to cancer, neutropenia, cancer chemotherapy</td>
<td>Myonecrosis, gas in tissues, systemic toxicity, shock</td>
</tr>
<tr>
<td>Necrotizing fascitis type 1</td>
<td>Mixed anaerobes, gram-negative aerobic bacilli, enterococci</td>
<td>Surgery, diabetes mellitus, peripheral vascular disease</td>
<td>Destruction of fat and fascia; skin may be spared; involvement of perineal area in Fournier gangrene</td>
</tr>
<tr>
<td>Necrotizing fascitis type 2</td>
<td><em>Group A streptococcus</em></td>
<td>Penetrating injuries, surgical procedures, variella, burns, minor cuts, trauma</td>
<td>Systemic toxicity, severe local pain, rapidly extending necrosis of subcutaneous tissues and skin; gangrene, shock, multorgan failure</td>
</tr>
</tbody>
</table>


Necrotizing fasciitis often is classified into three types. The polymicrobial form of the disease is described as necrotizing fasciitis type 1 and often occurs postoperatively or in patients with diabetes mellitus or peripheral vascular disease.66,69,79 Pathogens include gram-negative bacilli, enterococci, streptococci, *S. aureus* and anaerobes including *Bacteroides* spp., *Peptostreptococcus* spp., and *Clostridium* spp. (see Table 77-2). Necrotizing fasciitis type 2 is due to GAS infection that can occur postoperatively or as a result of penetrating trauma, variella infection, burns, or minor cuts; and is characterized by rapidly extending necrosis and severe systemic toxicity. Type 2 disease is the most common form of necrotizing fasciitis in children.70,72,80 Necrotizing fasciitis type 3 is rare and is caused by marine *Vibrio* spp., which enter through skin lesions that have been exposed to seawater or marine animals.

In children, necrotizing fasciitis often occurs 1 to 4 days after trauma, with soft-tissue swelling and pain over the affected area. Patients may appear well at initial presentation. When associated with variella, the findings typically begin 3 to 4 days after onset of the exanthem.3 Infants and toddlers may be fussy or irritable. Toddlers and young children may limp or refuse to bear weight. Initially, pain with manipulation of the affected extremity often is out of proportion to the cutaneous signs of infection.

Induration and edema generally are apparent within the first 24 hours and are followed rapidly by blistering and bleb formation.84,73,81 Infection spreads in the plane between the subcutaneous tissue and the superficial muscle fascia, which results in progressive destruction of fascia and fat (Figure 77-2). Pain and tenderness in the subcutaneous space are exquisite, but destruction of the nerves that innervate the skin eventually can lead to anesthesia of the overlying skin. The rapidly progressing infection can lead to toxic shock syndrome and severe systemic toxicity, including renal and hepatic failure, acute respiratory distress syndrome, and decreased myocardial contractility.

Extension of the infection along fascial planes leads to necrosis of the superficial fascia and the deeper layers of the dermis. Destruction and thrombosis of the small blood vessels in the area lead to necrosis of the surrounding tissues. The extensive tissue damage often leads to systemic symptoms, including multiorgan failure and shock.

Although white blood cell counts can be normal or elevated, there often is a pronounced shift to immature neutrophils. Thrombocytopenia and coagulopathy can occur. Attempts to identify causative organisms should be made through collection of anaerobic and aerobic blood cultures.59,75 Cultures of the wound and surgically debrided tissue should be obtained. Frozen section biopsies can be helpful in making a timely diagnosis.

**PART II Clinical Syndromes and Cardinal Features of Infectious Diseases: Approach to Diagnosis and Initial Management**

**SECTION J Skin and Soft-Tissue Infections**

**PATHOGENESIS**

Skeletal muscle tissue is intrinsically resistant to bacterial infections, likely due to sequestration by myoglobin of iron that is required for proliferating bacteria. *Staphylococcal* muscle infections appear to be a complication of transient bacteremia and typically develop without penetrating injury or other clear portal of entry. Blood cultures frequently are negative.62 Muscular trauma, strain, or vigorous exercise may be predisposing factors.53,81 The
high prevalence of the disease in the tropics has led to speculation that in patients with migrating parasitic infections, such as toxocariasis, microscopic foci of necrotic muscle develop that predispose to bacterial seeding. Alternatively, a viral infection can be the precipitant: ultrastructural studies of nonsuppurating lesions in some patients with tropical pyomyositis reveal intracellular particles and a lymphocytic infiltrate.

Group A streptococcal infection of skeletal muscle can take the form of a localized phlegmon, an abscess, or more fulminant necrotizing myositis or fasciitis, associated with septicemia and toxic shock syndrome. The association of invasive GAS with primary varicella infection may simply result from the full-thickness skin lesion of chickenpox, serving as a portal of entry for the organism (Figure 77-3). Varicella also produces a transient immunologic derangement, predisposing to secondary bacterial infection. A potential mechanism underlying the association of blunt trauma and streptococcal myonecrosis was provided by Bryant et al., who reported that muscle injury resulted in increased cellular vimentin expression, which enhanced colonization of GAS to the site of injury.

Both S. aureus and GAS express virulence factors, including adhesins, cytotoxins, superantigens, and immunomodulatory proteins, which contribute to the pathogenesis of infection. Although specific virulence factors are implicated in certain disease manifestations, such as superantigens as mediators of systemic toxicity and tissue injury, no single virulence factor is sufficient to provoke a severe staphylococcal or streptococcal infection. Rather a coordinated action of virulence factors is required in order for the bacteria to colonize successfully and spread within the host. Tissue injury and systemic toxicity are largely due to excessive inflammatory responses. A direct relation between the magnitude of the inflammatory response and severity of invasive GAS infections has been demonstrated. Although GAS usually is considered an extracellular organism, macrophages can be a reservoir for GAS during acute deep tissue infections. This may explain partially the persistent massive bacterial load despite adequate intravenous antibiotic therapy for a prolonged time in many patients.

Clostridium perfringens elaborates at least two exotoxins (α-toxin and perfringolysin O) that are cytolytic to host tissues and are lethal when purified and injected into animals. C. septicum also expresses a pore-forming cytotoxin, α-toxin, which triggers fulminant myonecrosis as well as inhibition of leukocyte influx into the lesion. Exotoxin-induced microvascular dysfunction is an important factor producing the anaerobic environment that favors C. perfringens replication and ischemic necrosis. By contrast, C. septicum is relatively aerotolerant, a feature that may partially explain its ability to spread through the bloodstream and establish infection in otherwise healthy muscle.

Figure 77-3. Necrotizing fasciitis of the abdominal wall due to Streptococcus pyogenes as a complication of chickenpox in a 7-year-old girl. Note dusky, ecchymosis, purpura, and edema of the abdominal wall (A). There was full-thickness necrosis of skin, subcutaneous tissue, and fascia (B). After multiple surgical debridements, the patient is ready for grafting (C). (Courtesy of J.H. Brien®.)

Figure 77-4. A 5-year-old girl experienced severe left posterior calf pain, tenderness, and swelling 1 week after onset of primary varicella. (A) With magnetic resonance imaging technique in which fat signal intensity is suppressed, marked signal enhancement is seen diffusely in the calf musculature, indicative of a widespread inflammatory process. (B) Operative exploration of the calf revealed liquefactive necrosis of the soleus muscle and the lateral head of the gastrocnemius muscle, which were radically debrided. Group A streptococcus was isolated from culture of tissue and blood. (Courtesy of J.H.T. Waldhausen, MD.)
## DIAGNOSIS

Early in the course, myositis, pyomyositis, or necrotizing fasciitis can be difficult to distinguish from a number of noninfectious disorders. Plain radiographs usually are normal, but other imaging techniques can be useful in defining the extent of muscle involvement. Although computed tomography (CT) may be useful in defining the extent of soft-tissue involvement, magnetic resonance imaging (MRI) is the preferred modality. MRI can reveal extension of inflammation along the fascial planes and distinguish compartments and structures (bone, muscle, fascia, fat) involved (see Figure 77-2).^{24,47} Ultrasoundography (US) is helpful in the suppurative phase.^{39,102,103}

CT or US may delineate a low-density (or hypoechoic) fluid collection, thereby facilitating diagnostic aspiration or percutaneous drainage.^{104,105} Diagnostic MRI findings include hyperintense signal within the muscle with edema in pyomyositis, and a hyperintense rim on unenhanced T1-weighted images and peripheral enhancement after intravenous infusion of gadolinium if abscess has formed.^{106} (see Figure 77-1). CT or MRI also can detect marked skeletal muscle abnormalities in GAS necrotizing myositis (Figure 77-4).^{103,107} Infrared thermography may help reveal the extent of tissue viability in clostridial myonecrosis.^{107}

## TREATMENT

Therapeutic interventions for SSTIs include incision, drainage, debridement, compartment release, and antibiotic therapy. Recommendations from both the Centers for Disease Control and Prevention^{66} and the American Academy of Pediatrics^{108} emphasize performing incision and drainage as the primary treatment of abscesses, sending purulent material for culture, and targeting CA-MRSA when empiric antibiotics are prescribed (Table 77-3). Effective surgical drainage of fluid collections or abscesses often can be accomplished percutaneously with ultrasound or CT guidance, but an open surgical procedure may be required.

Surgical debridement usually is necessary for GAS necrotizing pyomyositis once the patient has been stabilized medically.^{111} Fasciotomies are performed if there is evidence of increased compartment pressures. GAS uniformly is susceptible to penicillin and other β-lactam antibiotics, and penicillin remains an appropriate antibiotic treatment of GAS infections. However, in patients with aggressive GAS infections, such as myositis and necrotizing fasciitis, a β-lactam antibiotic should be combined with clindamycin (40 mg/kg per day) because of pharmacokinetic properties, activity at the ribosomal level, and inhibition of toxin production.

Therapy of clostridial gas gangrene consists of prompt and radical debridement of involved muscles; amputation may be required. Because 5% of strains of *C. perfringens* are clindamycin resistant, the recommended antibiotic treatment is penicillin plus clindamycin.^{111} Although the role of hyperbaric oxygen is controversial, therapy may serve an adjunctive role by retarding growth of *C. perfringens*, inhibiting α-toxin production, and increasing oxidative killing by host neutrophils.^{113} Patients who survive may require amputation, skin grafting, or reconstructive surgery.

In severe GAS infections, the use of high-dose immune globulin intravenous (IGIV) has been proposed as adjunctive therapy. The mechanism of action of IGIV in this setting is believed to include inhibition of the superantigen activity through neutralizing antibodies, opsonization through M-specific antibodies, and a general anti-inflammatory effect.^{114} Large controlled studies of IGIV therapy in patients with severe invasive GAS infections have not been conducted, but case reports and small controlled studies have reported use of IGIV in GAS toxic shock syndrome, necrotizing fasciitis, and necrotizing myositis (Table 77-4). A favorable outcome was reported for invasive GAS infections in an observational cohort study of Canadian patients identified through active surveillance^{115} and in one European multicenter placebo-controlled trial.^{116} Data on the efficacy of IGIV for necrotizing fasciitis are limited (see Table 77-4).^{117,118,119} In one study, mortality was 10% among IGIV-treated patients, compared with 37% in non-treated control subjects.^{117} In an observational case study, the use of an aggressive medical regimen including high-dose IGIV appeared to mitigate the need for aggressive surgical intervention.^{111} Seven patients with severe GAS soft-tissue infection (6 patients with toxic shock syndrome) were treated with antibiotics parenterally and high-dose IGIV; surgery was either not performed or limited to exploration; all patients survived. This limited study suggests that an initial conservative surgical approach combined with the use of immune modulators, such as IGIV, may reduce the morbidity associated with extensive surgical exploration in hemodynamically unstable patients.

Excellent guidelines available online from the Infectious Diseases Society of America provide empiric therapeutic options for specific clinical scenarios, i.e., dog bite, and specific pathogens of SSTIs.^{112}

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### TABLE 77-4. Intravenous Polyspecific Immunoglobulin (IGIV) as Adjunctive Therapy in Severe Invasive Group A Streptococcal Infections

<table>
<thead>
<tr>
<th>Study Design</th>
<th>No. of Patients</th>
<th>Case-Fatality Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NF and myonecrosis, case series identified through active surveillance</td>
<td>IGIV: 10</td>
<td>19</td>
</tr>
<tr>
<td>No IGIV: 4</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>NF, case series identified through active surveillance</td>
<td>IGIV: 10</td>
<td>10</td>
</tr>
<tr>
<td>No IGIV: 67</td>
<td>37</td>
<td></td>
</tr>
<tr>
<td>Severe soft-tissue infections, observational cohort study</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>STSS + NM, case report</td>
<td>IGIV: 10</td>
<td>0</td>
</tr>
<tr>
<td>Placebo: 11</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>STSS, case-control study</td>
<td>IGIV: 21</td>
<td>33</td>
</tr>
<tr>
<td>No IGIV: 32</td>
<td>66</td>
<td></td>
</tr>
</tbody>
</table>

*Study Design: NF, necrotizing fasciitis; NM, necrotizing myositis; STSS, streptococcal toxic shock syndrome; RCT, randomized control trial.

*All received IGIV unless otherwise specified.

* Trial prematurely terminated due to slow patient recruitment.

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### TABLE 77-3. Antimicrobial Agents for Treatment of Community-Acquired Methicillin-Resistant Staphylococcus aureus Infections in Children

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>Daily Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daptomycin^1</td>
<td>4–6 mg/kg per day q24 hours</td>
</tr>
<tr>
<td>Linezolid</td>
<td>30 mg/kg per day divided q6 hours</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>40 mg/kg per day divided q6 hours</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>10–30 mg/kg per day divided q6–8 hours</td>
</tr>
<tr>
<td>Trimethoprim/sulfamethoxazole</td>
<td>20 mg/kg per day divided q6 hours</td>
</tr>
<tr>
<td>Linezolid</td>
<td>30 mg/kg per day divided q6 hours</td>
</tr>
</tbody>
</table>

*Daptomycin should not be used to treat pneumonia; not approved by the Food and Drug Administration for the treatment of children.*
REFERENCES


