

Musculoskeletal Infections in Children

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Osteomyelitis

Introduction and epidemiology

Osteomyelitis is an infection of the bone and bone marrow generally of a bacterial origin. In the highly vascular bones of children, the most common form is acute hematogenous osteomyelitis (AHO). Approximately half of pediatric cases occur in children younger than 5 years of age [1–3], and boys are approximately twice as likely to be affected as girls [2,4]. The incidence has not been found to be higher in any one race than another [2,5]. Higher rates are seen in immunocompromised populations such as patients with sickle cell disease. Most cases occur in long bones. In a study of 163 infants and children with osteomyelitis [5], the femur, tibia, and humerus accounted for 68% of infections. Most cases are limited to a single site, with less than 10% involving two or more locations [2].

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Pathogenesis

Infection of bone may occur in several ways, including hematogenous spread, direct inoculation, and contiguous spread from a local infection [6,7]. In children, most cases result from hematogenous deposition of organisms in bone marrow after a transient episode of bacteremia. Approximately one third of patients report a history of blunt trauma [5], which may injure the bone and increase the likelihood of seeding the bone during bacteremia. Direct inoculation of bacteria into bone may occur during surgery or as a result of penetrating trauma, puncture wounds, or complex fractures.

Osteomyelitis most commonly begins in the metaphysis of long bones [6], which are highly vascular structures. In neonates, the metaphyseal capillaries form a connection with the epiphyseal plate. The periosteum is thin and does not adhere tightly to the underlying bone. As a result, the periosteum is more likely to perforate and spread infection into the surrounding tissues. Spread through the epiphysis also may result in septic arthritis and permanent growth plate damage (Fig. 1). The hips and shoulders are common sites of epiphyseal infection. In later infancy, the cortex thickens and the metaphyseal capillaries begin to atrophy, which decreases the risk of epiphyseal involvement and spread to local joint and soft tissue, although subperiosteal abscesses still form. In children and adolescents, the cortex is significantly thicker and infection in these patients rarely extends beyond the cortex.

Virulence factors of certain bacteria also favor the development of hematogenous osteomyelitis. *Staphylococcus aureus* bacteria adhere to bone by ex-



Fig. 1. (A) Radiograph of the left elbow of a 9-month-old child admitted for treatment of septic arthritis. The film revealed periosteal elevation in the distal portion of the humerus consistent with osteomyelitis. (B) MRI of the same patient revealed increased signal intensity on T2 images in the midpoint of the distal humerus, along with increased signal intensity in the distal humeral epiphysis.

pressing adhesins, which bind to a component of the bone matrix [7]. *S. aureus* also can survive intracellularly once internalized by osteoblasts [7]. Growing colonies of bacteria then surround themselves with a protective biofilm or glyco-calyx, which consists of exopolysaccharide polymers that allow ligand-receptor interaction and bonding of the bacteria to the substrate [8]. As the infection advances, cortical bone is destroyed and infection and inflammation may extend into the subperiosteal space. If the infection is left untreated, chronic osteomyelitis may develop, which is characterized by extensive tissue destruction caused by inflammatory cytokines that increase osteoclast activity and attract macrophages and monocytes. Necrotic cortical bone may separate and lead to the formation of a sequestrum, and new bone may form an incasing sheath around necrotic bone, known as an involucrum [6]. Inflammation also can lead to significant fibrosis.

Microbiology

In older infants and children, *S. aureus* is the most commonly identified organism and accounts for 61% to 89% of cases of AHO [5,9]. Group A β -hemolytic streptococci (GABHS) are next in frequency, and cause up to 10% of cases [10]. In the past, *Haemophilus influenzae* accounted for 3% to 7% of cases [1,5,9], but the advent of effective immunization has virtually eliminated this cause of osteomyelitis [10,11]. *Streptococcus pneumoniae* is another relatively common organism in patients with AHO. *Kingella kingae* is a common cause of osteomyelitis in the Middle East and is being recognized increasingly in the United States. Osteomyelitis caused by *K. kingae* tends to occur in young children after upper respiratory tract infections and stomatitis in the late summer through early winter [12]. Certain gram-negative bacteria are also known to cause AHO. *Salmonella* spp. are commonly identified in patients with sickle cell disease, and *Pseudomonas aeruginosa* is often identified in cases of osteochondritis after puncture wounds of the feet [13,14].

Although *S. aureus* is the most commonly reported organism in the neonatal age group, Group B streptococcus and enteric gram-negatives such as *Escherichia coli* are also common [15]. Mycobacteria and fungi are rare causes of osteomyelitis [14]. *Bartonella henselae* is an atypical cause of osteomyelitis in patients with cat-scratch disease [16,17]. Polymicrobial infection is rare and is seen most commonly in cases of puncture wounds or other trauma.

Clinical presentation

Older children and adolescents often present after days to weeks of symptoms and most commonly complain of pain at the affected site and fever. The pain is typically constant and well localized. Infants and toddlers may present with irritability, refusal to bear weight or use an extremity, or limp. In younger patients, subperiosteal spread may lead to erythema, warmth, and swelling of the

affected site. Young patients also may present with fever of unknown origin because they are unable to localize pain.

Neonates with osteomyelitis may present with pseudoparalysis and significant tenderness with palpation of the affected site [15]. They often have a history of a preceding infection, and approximately one third have multiple sites involved [18]. Neonates are also at higher risk of concomitant joint infection compared with older patients [2,18].

Differential diagnosis

The differential diagnosis for osteomyelitis includes cellulitis, septic arthritis, toxic synovitis, thrombophlebitis, trauma, fracture, rheumatologic diseases (eg, juvenile rheumatoid arthritis), pain crisis in sickle cell disease, Ewing's sarcoma, osteosarcoma, and leukemia.

Diagnosis and evaluation

Blood tests are often supportive but not specific for osteomyelitis. A complete blood count may reveal leukocytosis, but it may be normal, especially in chronic cases [6]. In a study of 44 children with AHO, only 35% had leukocytosis at the time of admission [9]. Inflammatory markers, such as the erythrocyte sedimentation rate and C-reactive protein, are elevated in more than 90% of patients [5,9] and can be used to follow response to therapy. The C-reactive protein and erythrocyte sedimentation rate often continue to rise in the first 2 to 5 days after initiation of therapy and return to normal within 1 (C-reactive protein) to 3 (erythrocyte sedimentation rate) weeks [9].

Identification of an organism is critical to confirming the diagnosis and guiding antimicrobial selection. Needle aspiration is likely to yield an organism in approximately two thirds of cases [3,5], whereas blood cultures yield positive results in 36% to 55% of specimens [2,3]. Open procedures that involve metaphyseal drilling may enhance the yield and may be therapeutic.

The value of plain films (Table 1) depends on the duration of active disease, and in most patients the infection is clinically localizable before radiologic

Table 1
Advantages and disadvantages of various imaging modalities for osteomyelitis

Modality	Advantages	Disadvantages
Plain film	Inexpensive, quick, easy	Insensitive in early disease
CT	Improved sensitivity, relatively quick	Radiation exposure, may require sedation
MRI	Very sensitive, even in early disease, may reveal pus collections or extension into adjacent joint or soft tissue	Long study, often requires sedation, expensive
Bone scan	Very sensitive, identifies multifocal disease, may reveal unsuspected sites in preverbal children	Less specific, long study, often requires sedation, expensive, radiation exposure

changes are evident on radiographs [19]. In the first 3 days, plain films may reveal localized soft-tissue swelling. By days 3 to 7, swelling of the surrounding muscle may lead to obliteration of the normally visible fat planes. Osteolytic lesions are generally not apparent until there has been more than 50% loss of bone density [20]—often 2 weeks or more after initial symptoms—and periosteal reaction is not evident until days 10 to 21 of illness [5,21].

Nuclear scintigraphy is helpful in young patients who are unable to verbalize the location of their pain, when multiple sites are suspected, and in differentiating osteomyelitis from cellulitis. The technetium 99m methylene diphosphonate bone scan is the most commonly ordered nuclear imaging procedure (Fig. 2) [21]. After injection, there is immediate distribution to areas of hyperemia; later imaging demonstrates increased uptake in areas of osteoclastic/osteoblastic activity. It is sensitive for the detection of early osteomyelitis [7] but is not specific for infection. Tagged leukocyte scans (eg, indium 111 or technetium 99m) can be used but require special technical skills and may yield false-positive results.

Cross-sectional imaging may be necessary to distinguish associated soft-tissue infection, delineate the extent of bone involvement, and help plan surgical management [22]. CT can reveal areas of cortical bone destruction, periosteal reaction, sequestration, and soft-tissue abscesses. Images should be obtained with and without enhancement.

With a reported sensitivity of 97% [23], MRI is becoming the modality of choice in patients with a strong suspicion of osteomyelitis [24]. The high resolution makes it useful for differentiating between bone and soft-tissue infection [6]. Edema and exudate of the medullary space may be noted in the initial stages of osteomyelitis (Fig. 3), which allows for early diagnosis. Coronal

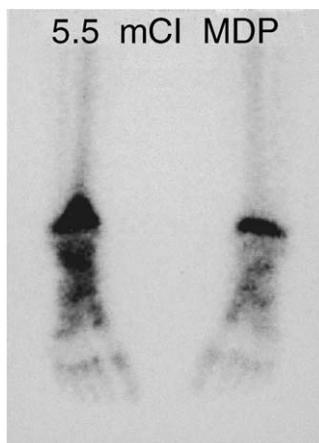


Fig. 2. Three-phase bone scan of a 1-year-old boy who presented with fever and a painful right lower extremity. Flow images revealed increased flow to the right lower extremity with increased activity to the distal metaphysis of the right tibia. Blood pool images showed increased radiotracer uptake to the distal metaphysis of the right tibia.



Fig. 3. MRI image of a 1-year-old boy with 3 weeks of right hip pain. There is marked abnormal increased signal intensity in the posterior aspect of the right ischium on the T2-weighted images, compatible with marrow edema and consistent with osteomyelitis. Extensive edema and inflammation also are seen in the right obturator internus muscle and in the gamellus muscles posterolateral to the right ischium.

or sagittal images are especially useful for planning surgical procedures and assessing the growth plates and epiphyses. Gadolinium enhancement is recommended to improve sensitivity [21].

Management

Treatment of osteomyelitis initially requires inpatient management with a combination of antibiotic therapy and possible surgical procedures [1,5–7,20]. Upon admission, an orthopedic surgeon should be consulted, especially if imaging reveals subperiosteal or soft-tissue abscesses, sequestra, or intramedullary purulence. A surgeon's roles include performing diagnostic needle aspiration, decompression and drainage (when necessary), and long-term follow-up in complicated cases. Surgical intervention is reported to be required in approximately 50% of cases [2,5], although some authors recommend a more conservative approach [3].

Empiric medical therapy should cover *S. aureus* and GABHS, and traditionally, a semi-synthetic penicillinase-resistant penicillin was recommended (eg, nafcillin or oxacillin, 150–200 mg/kg/d, divided in four doses). Several recent reports have indicated a sharp increase in the number of cases of community-acquired methicillin-resistant *S. aureus* infections, however [25]. In communities with a high incidence of community-acquired methicillin-resistant *S. aureus*, vancomycin should be considered for empiric therapy of osteomyelitis until sensitivities are available. Alternatively, clindamycin may be effective against community-acquired methicillin-resistant *S. aureus* [26], but inducible resistance may reduce its effectiveness. This resistance can be detected using a D-test performed by the microbiology laboratory. In infants and children up to 5 years of age, a second- or third-generation cephalosporin (eg, cefuroxime, cefotaxime,

ceftriaxone) provides coverage against many *S. aureus*, most streptococci, and *K. kingae*.

Empiric therapy in neonates should cover Group B streptococcus and enteric gram-negative bacilli in addition to the pathogens common in older infants and children. In neonates, cefotaxime may be used for empiric therapy, and coverage can be narrowed once culture results and sensitivities are available.

In patients with presumed pseudomonal infection (eg, puncture wound osteochondritis of the foot), one should consider an extended spectrum beta-lactam (eg, ceftazidime, cefepime, piperacillin/tazobactam) plus an aminoglycoside for at least the first 2 weeks.

Once an organism has been identified, coverage can be narrowed based on results of susceptibility testing. The minimum recommended length of treatment is 3 weeks because of the increased likelihood of developing chronic osteomyelitis if the length of therapy is shortened [27]. Most authors recommend treatment for 4 to 6 weeks [28]. If long-term intravenous antibiotics are administered, placement of a peripherally inserted central catheter should be considered for completion of the regimen as an outpatient. Several studies support switching to an oral antibiotic if there is a high likelihood of compliance, an organism has been identified, clinical improvement is noted, the patient is afebrile, and inflammatory markers have begun to normalize after the first week of parenteral therapy [2,3,29,30].

When changing to oral antibiotics, doses of two to three times those normally recommended are often used. Some authors recommend following weekly serum bactericidal titers to ensure that adequate blood levels are achieved [3]. To measure bactericidal titers, a patient's blood is drawn 1 to 2 hours after administration of the antibiotic and testing is performed to establish the highest dilution of the patient's serum, which kills 99.9% of inoculated bacteria after 18 hours of culture. Dilutions of at least 1:8 are desirable [3]. More recently, Marshall et al [31] questioned the need for serial bactericidal titers in patients treated with oral antibiotics for skeletal infections, and many microbiology laboratories no longer perform this procedure.

Special considerations

Chronic osteomyelitis

Up to 19% of patients with AHO who are inadequately treated may develop chronic osteomyelitis compared with 2% of patients who receive antibiotic therapy for longer than 3 weeks [5]. Chronic osteomyelitis is characterized by a chronic, suppurative course with intermittent acute exacerbations. This may occur after an open fracture or when subperiosteal or metaphyseal pus is not adequately drained. Treatment is often difficult and involves long-term antibiotics, sometimes up to 6 to 12 months, often in combination with one or more surgeries for débridement. The extensive surgical debridement may necessitate reconstructive surgery with bone grafts and muscle flaps [27].

Brodie abscess

A Brodie abscess is a subacute form of osteomyelitis that results in a collection of necrotic bone and pus in a fibrous capsule, which is formed by surrounding granulation tissue [27]. It occurs most commonly in the long bones of adolescents. The defect may be seen on plain film, and on MRI it has a distinctive target appearance. Although the erythrocyte sedimentation rate is usually elevated, it may be normal. Management involves surgical drainage followed by antibiotic therapy. Properly treated patients have a good prognosis.

Osteomyelitis in patients with sickle hemoglobinopathies

Osteomyelitis in patients with sickle cell disease may be difficult to differentiate from a vaso-occlusive crisis. Both syndromes can present with fever, bone pain, and tenderness. Spiking fevers above 39°C, chills, toxic appearance, and leukocytosis are more concerning for osteomyelitis in this population. Infection can be difficult to differentiate from infarction on imaging studies, and needle aspiration or biopsy of the affected site may be required. In addition to *S. aureus*, *Salmonella* spp. are common etiologic agents [32], and empiric therapy (eg, a cephalosporin, possibly in combination with vancomycin) should be chosen accordingly. Prolonged parenteral therapy (at least 6–8 weeks) is often required.

Pseudomonas osteochondritis

Up to 2% of nail puncture wounds of the foot are complicated by osteochondritis, and *P. aeruginosa* is the infecting organism in most cases [14]. *P. aeruginosa* can be found in the liner of sneakers, although infections may occur after puncture wounds through other types of shoes or even bare feet. Management generally involves surgery to remove necrotic cartilage and obtain specimen for culture. After adequate debridement, an intravenous antibiotic with pseudomonas coverage and coverage of the more common pathogens (eg, cefepime or piperacillin/tazobactam) is generally used for 7 to 14 days. Although adult studies seem to indicate that oral ciprofloxacin for 7 to 14 days is usually adequate [14], some authors believe that intravenous therapy should be used in pediatric cases [33,34]. Anecdotally, the use of prophylactic ciprofloxacin in patients with puncture wounds may prevent the development of osteochondritis.

Spinal osteomyelitis

Osteomyelitis of the spine may be in the form of discitis or vertebral osteomyelitis. Discitis is an inflammatory process, usually of a lumbar disc, that is most common in children younger than 5 years of age (mean age, 2.8 years) [16]. Discitis generally results from low-grade bacterial infection, although some authors believe that it can be noninfectious (eg, after trauma to the spine). Patients may present with a limp, backache, or refusal to walk. Fevers are generally absent or low grade. Plain films may demonstrate narrowing of the disc space. Antibiotic therapy should cover *S. aureus* and GABHS and may be given orally for the entire course or intravenously for 5 to 7 days followed by oral administration for another 7 to 14 days.

Vertebral osteomyelitis occurs in 1% to 2% of cases of osteomyelitis and tends to occur in slightly older children (mean age, 7.5 years) [16]. It may result from hematologic seeding of the vertebrae or through extension of a local infection, such as discitis. *S. aureus* is the most common organism, but other organisms, including *Bartonella henselae* (cat-scratch disease), have been reported [16]. In some areas of the world, tuberculous spondylitis (Pott disease) is not uncommon [35]. Patients with Pott disease may manifest with kyphosis and neurologic deficits. Diagnosis of vertebral osteomyelitis is often based on MRI. Surgery may be required urgently if there is evidence of spinal cord compression. Antibiotics should be administered for at least 4 weeks.

Chronic recurrent multifocal osteomyelitis

Chronic recurrent multifocal osteomyelitis is characterized by recurrent episodes of bony inflammation, pain, and fever with periodic exacerbations and remissions [27]. Culture results are negative, and antibiotics have not been found to alter the course of the disease. Chronic recurrent multifocal osteomyelitis presents most commonly in children and adolescents, with a mean age at presentation of 14 years [36]. Chronic recurrent multifocal osteomyelitis is associated with Sweet syndrome (ie, acute febrile neutrophilic dermatosis), psoriasis, and pustulosis palmaris et plantaris. Plain films may demonstrate multiple areas of osteolysis and sclerosis, especially in the long bones and clavicles. Treatment generally involves glucocorticoids and nonsteroidal anti-inflammatory drugs. Other reported therapies include immune modulators, antimetabolites, calcium modulators, colchicine, and hyperbaric oxygen.

Septic arthritis

Introduction and epidemiology

Septic arthritis refers to bacterial invasion of the joint space and the subsequent inflammatory response. Septic arthritis is commonly a disease of childhood, with approximately half of all cases occurring in patients younger than 20 years of age [37]. Rates of septic arthritis are estimated to be between 5.5 and 12 cases per 100,000 children [38]. The peak incidence is in children younger than 3 years, and boys are affected approximately twice as often as girls [37–39]. Septic arthritis occurs more commonly in patients with diabetes mellitus, sickle cell disease, and immunodeficiencies. The most commonly affected joints are those of the lower extremities, including knees, hips, and ankles, which account for up to 80% of cases [37,40,41].

Pathogenesis

There are several mechanisms by which bacteria may be introduced into the synovial fluid. Septic arthritis may occur as a result of hematogenous seeding of

the synovium during a transient episode of bacteremia, from contiguous spread of an adjacent infection such as osteomyelitis, or by direct inoculation during surgery or as a result of penetrating trauma. Characteristics of the joint, which increase the likelihood of infection during bacteremia (hematogenous spread), include the highly vascular nature of synovium and the lack of a limiting basement membrane, which may allow bacteria to enter the joint space more readily. Several strains of *S. aureus* also have collagen receptors on their surface.

Once the joint space is invaded by bacteria, endotoxins are released. In response to these endotoxins, cytokines, such as tumor necrosis factor and interleukin-1, are released, which in turn stimulate the release of proteolytic enzymes and increase leukocyte migration [42,43]. This combination of factors leads to destruction of the synovium and cartilage matrix. Although cases of septic arthritis rarely have been fatal since the introduction of antibiotics, destruction of the joint space leads to long-term sequelae in a significant percentage of patients [44,45].

Some joints are more susceptible to damage. For example, increased pressure within the hip can interrupt blood flow and lead to avascular necrosis of the femoral head. Prompt recognition and aggressive management are critical.

Microbiology

The specific bacteria isolated from joint fluid in patients with septic arthritis vary with age. In all age groups outside of the neonatal period, *S. aureus* is the most common organism [39,45,46]. Other frequently identified organisms include GABHS and *S. pneumoniae*. In the neonatal period, *S. aureus* remains a common organism, but group B streptococcus is also frequently identified [47,48]. Neonates are also at risk for gram-negative enteric bacilli. Neonates and sexually active adolescents are at risk for infection by *Neisseria gonorrhoeae* [49].

Currently an unusual cause of septic arthritis, *H. influenzae* type B commonly was identified before the introduction of an effective vaccine [41,44,46]. *K. kingae* may be identified in toddlers with a preceding history of an upper respiratory tract infection [50]. In addition to the usual organisms, patients with sickle cell disease are at risk for bone and joint infections by *Salmonella* spp. *Neisseria meningitidis* is a rare cause of septic arthritis but is commonly associated with reactive arthritis. *P. aeruginosa* also has been reported as a causative agent [51].

Clinical presentation

Patients with septic arthritis usually present with focal findings at the infected joint. Symptoms include edema, erythema, joint effusion, and tenderness. Patients tend to keep the affected joint in a position that maximizes intracapsular volume and comfort. Knees are held moderately flexed, and hips are kept flexed, abducted, and externally rotated. Refusal to move an affected joint is referred to

as pseudoparalysis, and even passive movement may be painful. Systemic symptoms such as fever, malaise, and poor appetite are also seen in most patients. The progression of the disease is rapid, with many patients having symptoms for no more than 72 hours before diagnosis.

Diagnosis in neonates is often more difficult. Inflammation may be less impressive because of an immature immune system. The hip, the most commonly affected joint in neonates [40,44,48], is deep, and any present inflammation may be disguised. Discomfort may be noted with diaper changes and other manipulation of the hip.

In all age groups, approximately 75% to 80% of cases involve joints of the lower extremities, with the knees and the hips being most commonly affected [37,39,40]. Other commonly affected joints include the ankles, wrists, elbows, and shoulders. Small, distal joints are less likely to be involved. Polyarticular joint involvement occurs in less than 10% of patients but is seen in up to 50% of patients with infection caused by *N. gonorrhoeae* [37,40,44,46].

Differential diagnosis

Multiple entities may be confused with septic arthritis, including hemarthrosis, traumatic effusion, transient synovitis, reactive arthritis, Lyme arthritis, juvenile rheumatoid arthritis, arthritis of acute rheumatic fever, osteomyelitis, tumor, slipped capital femoral epiphysis, and Legg-Calvé-Perthes disease. In particular, transient synovitis (also known as toxic synovitis) often mimics septic arthritis. Transient synovitis is presumed to be a postviral phenomenon and often affects the hip in boys between the ages of 3 and 10 years. The arthritis that occurs with Lyme disease is also a great imitator of septic arthritis and must be considered in endemic areas. Multiple bacteria, including *N. meningitidis*, *Streptococcal* spp., *Salmonella* spp., and *Mycoplasma pneumoniae* are associated with postinfectious reactive arthritides. In cases of suspected septic arthritis, concomitant osteomyelitis of an adjacent bone should be suspected.

Diagnosis and evaluation

The cornerstone of diagnosis is the evaluation of aspirated joint fluid. The fluid should be sent for gram stain, aerobic culture, and cell count with differential [52]. Typical findings of aspirated synovial fluid are presented in Table 2. An organism is isolated from culture of joint fluid in approximately 60% of cases [41,45], which allows for definitive diagnosis and narrowing of antibiotic coverage. Synovial fluid should be aspirated into a heparinized syringe. *K. kingae* is a slow-growing fastidious organism. If it is suspected, synovial fluid should be inoculated directly into a blood culture bottle, which increases the yield [50].

Blood cultures produce positive results in one third of cases and may help identify the pathogen in cases where the synovial culture fluid is negative [41,45]. In general, the white blood cell count, C-reactive protein, and erythrocyte sedi-

Table 2
Typical synovial fluid findings

	Septic arthritis	Transient synovitis	Normal joint
Color	Serosanguinous	Yellow	Yellow
Clarity	Turbid	Generally clear, but depends on number of white blood cells	Clear
White blood cells	>50,000–100,000/mm ³	5,000–15,000/mm ³	<200/mm ³
% Polymorphonuclear neutrophils	>75%	<25%	<25%
Culture	Positive in 60%	Negative	Negative
Glucose	<40 mg/dL	Equal to serum	Equal to serum

mentation rate are elevated in patients with septic arthritis, but some patients present with normal inflammatory markers [44,45,53,54].

Imaging studies also may be helpful in making the diagnosis but should not delay aspiration of the joint or the prompt surgical and antibiotic management in cases in which septic arthritis is suspected. Plain films may demonstrate a widened joint space in a patient with a septic hip but are more useful for ruling out other conditions, such as fractures, Legg-Calvé-Perthes disease, and slipped capital femoral epiphysis. Ultrasonography is useful in identifying and quantifying a joint effusion, especially in deeper joints, such as the hips, and may be used to guide needle aspiration of these joints (Fig. 4) [54,55]. Bone scan and MRI are often used and may play a critical role in diagnosing concomitant osteomyelitis [55].



Fig. 4. Sonographic evaluation of the hips in an 11-year-old boy with fever and right hip pain. Moderate effusion of the right joint space that measured 1.3 cm is noted.

Management

Antibiotic therapy should be initiated immediately after blood and synovial fluid cultures have been obtained. Antibiotics have good penetration into the synovial fluid, with several studies finding equal concentrations in the joint fluid and serum 1 hour after administration [56–58]. The gram stain can help guide the initial antibiotic choice; however, the antibiotic therapy should not be delayed if this result cannot be obtained promptly. If gram-positive cocci are seen, empiric therapy with a semi-synthetic, penicillinase-resistant penicillin (eg, oxacillin, 150 mg/kg/d, divided in four doses) is the traditional choice. Vancomycin or clindamycin should be considered in areas with high rates of community-acquired methicillin-resistant *S. aureus*, however (see previous discussion). If Gram stain reveals gram-negative organisms or if no organisms are seen, one should consider a third-generation cephalosporin, such as cefotaxime or ceftriaxone, which covers most gram-positive organisms and *K. kingae*, *Salmonella* spp., and *H. influenzae*. In sexually active adolescents, ceftriaxone or cefotaxime may be used to cover *N. gonorrhoeae*. Neonates are often treated with oxacillin or nafcillin plus cefotaxime or gentamicin, although cefotaxime alone covers the most likely etiologic agents. Coverage can be narrowed once identification of the organism and susceptibilities are available.

Most authors agree that septic arthritis of the hip is a medical emergency that requires immediate surgical drainage. Infants with septic arthritis of the shoulder are also treated with emergent surgical drainage. When other joints are affected, some authors advocate repeated, daily aspiration, which has proved to be superior to surgical drainage in an adult study [59]. If a large amount of fibrin or debris is present, the infection is loculated, or there is a lack of improvement within 3 days, however, then surgical drainage is recommended. Physical therapy may be beneficial as adjunctive management in some cases, especially when a child is hesitant to use the joint.

In uncomplicated cases, the total duration of therapy should be at least 3 weeks, with at least 1 week of antibiotics given intravenously. If a patient improves clinically after 1 week and inflammatory markers are normalizing, then the remaining 2 weeks of antibiotics can be given orally. Despite appropriate management, approximately 40% of patients with hip involvement and 10% of patients with knee involvement suffer significant sequelae, such as growth plate damage and loss of function [44,45,60]. Close follow-up in all patients and physical therapy in selected patients are essential.

Pyomyositis

Introduction and epidemiology

Pyomyositis is a bacterial infection of skeletal muscle with a predilection for large muscle groups, and it often results in localized abscess formation. Although

relatively uncommon in more temperate areas, such as North America [61], pyomyositis accounts for up to 4% of surgical admissions in some tropical areas [62]. This geographic distribution has led to the alternative name of pyomyositis tropicans. Within North America, the highest incidence of pyomyositis is in the southernmost regions. In children, the peak incidence seems to occur between 5 and 9 years of age [63].

Pathogenesis

Pyomyositis is believed to occur when a transient bacteremia seeds a site of local muscle trauma or strain [64,65]. Patients with pyomyositis are able to recall a history of trauma in only approximately 25% of cases, however [66,67]. Vigorous exercise, presumably a cause of muscle strain, also may be a causative factor [68,69]. Other authors have suggested that an antecedent viral infection may be a predisposing factor in some cases [66].

Microbiology

S. aureus is the most commonly identified organism; it accounts for approximately 90% of cases of pyomyositis in tropical areas [66,67] and approximately 70% of cases in North America [70]. **Box 1** lists other reported causes. Clostridial infections can lead to a fulminant form of myonecrosis, which is often fatal [71].

Box 1. Reported causes of pyomyositis

S. aureus
Group A streptococcus
Other *Staphylococcal* and *Streptococcal* spp.
E. coli
Salmonella enteritidis
Citrobacter freundii
Clostridium spp.
Serratia spp.
Klebsiella spp.
Yersinia spp.
Pasteurella spp.
Mycobacterium tuberculosis
Candida albicans

Data from references [1,3,4,8,13–15].

Clinical presentation

The initial presentation of pyomyositis is often subacute, and initial symptoms may be vague. In a review of 16 cases of pyomyositis in children [72], the mean duration of symptoms before presentation was 8.9 days. Patients presented with pain (100%), fever (93.8%), swelling (62.5%), and limp (100% of lower body abscesses).

Pyomyositis occurs in three stages [70,73,74]. The invasive stage is characterized by low-grade fevers, general malaise, and dull, cramping pain. Although the overlying skin often appears normal, a firm or “woody” texture may be appreciated on deep palpation. Abscess formation occurs during the suppurative stage, and patients tend to have more focal complaints. Often there is increased tenderness with overlying erythema and swelling. During the late stage of pyomyositis, patients develop high fevers, exhibit more local signs of infection, and complain of severe pain. Patients in the late stage of pyomyositis can develop systemic manifestations, including metastatic abscesses, arthritis, and renal failure. Septic shock and toxic shock may ensue if urgent management is not initiated. Although rare, death has been reported after this late stage of pyomyositis [66].

Pyomyositis most commonly affects the quadriceps, gluteal, and iliopsoas muscles [66]. Other affected areas include the paraspinus, psoas, shoulder girdle, extremities (eg, gastrocnemius), chest wall, and abdominal wall [66,72–75]. Patients with psoas muscle involvement may present with limp, hip pain, or back pain. Multiple sites are involved in 11% to 43% of patients [66,67].

More rapidly necrotizing infections of muscle also have been described. Infections with GABHS [76] often occur in patients with a primary varicella infection and can cause a rapidly progressive, necrotizing form of pyomyositis (see the later discussion on necrotizing fasciitis). Within hours of presentation, patients can develop hypotension, oliguria, lethargy, and toxic shock. A scarlatiniform rash may be present.

Clostridial myonecrosis (gas gangrene) generally occurs 2 to 3 days after wound contamination with *Clostridium perfringens* and is characterized by myonecrosis, gas production, and sepsis. Patients may present initially with localized pain and pallor [77]. Subcutaneous emphysema and crepitus may be appreciated. Symptoms may progress rapidly with the appearance of hemorrhagic bullae and the development of cutaneous necrosis, acidosis, coagulopathy, and shock.

Differential diagnosis

In a review of 97 cases of pyomyositis in adults, erroneous diagnoses at admission included thrombophlebitis (7 cases), sarcoma or malignancy (7 cases), cellulitis (3 cases), osteochondritis (1 case), contusion (1 case), and compartment syndrome (1 case) [78]. The broad differential diagnosis of pyomyositis also

includes other infectious processes, such as septic arthritis, acute appendicitis, and osteomyelitis. Other inflammatory processes that may mimic pyomyositis include polymyositis, bursitis, and other rheumatic diseases. Pyomyositis also may be confused with muscle strain, viral myositis (eg, influenza, enterovirus), deep venous thrombosis, or hematoma.

Diagnosis and evaluation

Ultrasonography is a quick and inexpensive study that can detect muscle abscesses [79] and may be used to guide percutaneous drainage. Alternatively, CT can provide good delineation of muscle structure and may demonstrate a fluid collection. MRI with gadolinium is the most sensitive study for detecting early inflammatory changes. MRI also can define the extent of muscle involvement and may help identify patients with early disease who do not require surgical intervention [73].

Laboratory studies tend to be nonspecific. A complete blood count generally demonstrates a leukocytosis with a left shift. Eosinophilia is more common in patients from the tropics [73] and may represent concomitant parasitic infection. The erythrocyte sedimentation rate is often elevated [78]. Muscle enzymes, such as creatine kinase and aldolase, are generally normal. In one study, blood cultures yielded positive results in 29% of cases [80]. Fluid aspirated from the site of infection is more likely to yield an organism.

Management

Surgical incision and drainage are generally required, although certain patients who present with muscle inflammation but do not yet have abscess formation may be managed with antibiotic therapy alone [73,74]. CT [81] or ultrasound-guided percutaneous drainage is another alternative to surgical management in some patients.

Because *S. aureus* accounts for most infections, a semi-synthetic penicillinase-resistant penicillin (eg, nafcillin or oxacillin, 150 mg/kg/d, divided every 6 hours) is the traditional choice for empiric therapy. Clindamycin is an alternative, especially in patients with penicillin allergies, and vancomycin should be considered for empiric therapy in areas with a high incidence of community-acquired methicillin-resistant *S. aureus* (see discussion in the section on osteomyelitis).

The optimal length of therapy is not well described. In general, intravenous antibiotics should be continued until clinical improvement is evident. Based on sensitivities, appropriate oral antibiotics should be continued for a total of 2 to 6 weeks [66,73,74].

Necrotizing GABHS infections require immediate surgical exploration/debridement and possible fasciotomy. Therapy should include clindamycin for the Eagle effect [82] (see the section on necrotizing fasciitis) because most cases

of pyomyositis are diagnosed after the organisms have reached a steady-state growth phase.

Necrotizing fasciitis

Introduction and epidemiology

Necrotizing fasciitis (also known as hospital gangrene or hemolytic streptococcal gangrene) was described as early as the fifth century BC, when Hippocrates wrote, “flesh, sinews and bones fell away in large quantities. The flux which formed was not like pus but a different sort of putrefaction with a copious and varied flux. . . There were many deaths” [83]. Necrotizing fasciitis is a rapidly progressive, deep-seated bacterial infection of the subcutaneous soft tissue that may involve any area of the body. It often follows a fulminant course and has a high mortality rate. Estimates of the mortality rate range from 25% to 75% [84,85].

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 [86,87]. Men are affected slightly more commonly than women [84,85,88]. An increased frequency is reported in persons with diabetes, intravenous drug users, alcoholics, immunosuppressed patients, and patients with peripheral vascular disease [85,86,88]. Necrotizing fasciitis also occurs in young, previously healthy patients, including children. Mortality rates in children and previously healthy individuals tend to be much lower [86].

Pathogenesis

Necrotizing fasciitis begins with the introduction of bacterial infection. Extension of the infection along fascial planes leads to necrosis of the superficial muscle 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.

Predisposing factors include trauma, surgery, burns, and eczema [84]. In neonates, necrotizing fasciitis may complicate omphalitis or circumcision. Less commonly associated factors include insect bites, perirectal abscesses, incarcerated hernias, and subcutaneous insulin injections. Necrotizing fasciitis has been reported in several cases as a complication of varicella infection [86,89,90]. Necrotizing fasciitis also may occur with a preceding GABHS pharyngitis or without any previous evidence of trauma or infection.

An association between the use of nonsteroidal anti-inflammatory drugs and necrotizing fasciitis has been reported [89,91,92]. Given the frequency of nonsteroidal anti-inflammatory drug use worldwide, however, most authors believe

that patients with necrotizing fasciitis are likely to have taken the drugs for their analgesic and anti-inflammatory properties and that a true cause-and-effect relationship is unlikely [92].

Microbiology

Necrotizing fasciitis is often polymicrobial in origin [84,85,93] and involves gram-negative bacilli, enterococci, streptococci, *S. aureus* and anaerobes such as *Bacteroides* spp, *Peptostreptococcus* spp, and *Clostridium* spp (Table 3). This polymicrobial form of the disease is described as necrotizing fasciitis type 1 and is often seen postoperatively or in patients with diabetes mellitus or peripheral vascular disease. Gas gangrene is the result of clostridial infection (*C. perfringens*, *C. histolyticum*, *C. septicum*) often secondary to trauma or crush injury. It is a myonecrotic disease that quickly leads to systemic toxicity and shock.

Necrotizing fasciitis type 2 is an infection with GABHS that may occur postoperatively or as a result of penetrating trauma, varicella infection, burns, or minor cuts. It is characterized by rapidly extending necrosis and severe systemic toxicity. Type 2 disease is the most common type in children with necrotizing fasciitis [86,88,94].

Less common than type 1 or type 2, necrotizing fasciitis type 3 is caused by marine *Vibrio* spp., which enter through skin lesions that have been exposed to seawater or marine animals.

Table 3
Bacteria associated with necrotizing fasciitis [84,85,93]

Category	Organism
Gram-positive aerobes	Group A beta-hemolytic streptococcus
	<i>S. aureus</i>
	Other staphylococcal and streptococcal spp.
Gram-negative aerobes	Enterococci
	<i>E. coli</i>
	<i>P. aeruginosa</i>
	<i>Enterobacter cloacae</i>
	<i>Klebsiella</i> spp.
	<i>Proteus</i> spp.
	<i>Serratia</i> spp.
	<i>Acinetobacter calcoaceticus</i>
	<i>Citrobacter freundii</i>
	<i>Pasteurella multocida</i>
Anaerobes	<i>Bacteroides</i> spp.
	<i>Clostridium</i> spp.
	<i>Vibrio</i> spp.
	<i>Peptostreptococcus</i> spp.

Data from references [84,85,93].

Clinical presentation

Patients may report a history of recent surgery, trauma, omphalitis, or varicella infection [89,90]. In children, necrotizing fasciitis often presents 1 to 4 days after trauma with soft-tissue swelling and pain near the infected area. Patients may appear well at initial presentation. When associated with varicella, the findings typically begin 3 to 4 days after onset of the exanthem [90]. Infants and toddlers may be fussy or irritable. Toddlers and young children may present with a limp or refusal to bear weight. Initially, pain with manipulation of an affected extremity tends to be out of proportion to the cutaneous signs of infection.

Induration and edema are generally apparent within the first 24 hours and are followed rapidly by blistering and bleb formation [95,96]. Infection spreads in the plane between the subcutaneous tissue and the superficial muscle fascia, which results in the progressive destruction of fascia and fat. The skin takes on a dusky appearance, and a thick, foul-smelling fluid is produced. Pain and tenderness in the subcutaneous space is exquisite and often seems out of proportion to the cutaneous appearance, but destruction of the nerves that innervate the skin may lead to anesthesia of the overlying skin. High fevers are common. The rapidly progressing infection can lead to toxic shock syndrome and severe systemic toxicities, including renal and hepatic failure, acute respiratory distress syndrome, and decreased myocardial contractility.

Differential diagnosis

The differential diagnosis of necrotizing fasciitis includes other soft-tissue infections, such as cellulitis, pyomyositis, and gas gangrene. In cases of Fournier's gangrene, hernias, epididymitis, orchitis, and testicular torsion also must be considered.

Diagnosis and evaluation

Although white blood cell counts may be normal or elevated, there is often a pronounced bandemia. Thrombocytopenia and evidence of a coagulopathy also may be apparent. Attempts to identify causative organisms should be made through collection of anaerobic and aerobic blood cultures, although the results are frequently negative [85,90]. Cultures of the wound and surgically debrided tissue also should be taken. Frozen section biopsies can be helpful in making a timely diagnosis.

Radiologic studies may support the diagnosis, but they should not delay surgical intervention. Plain films may show gas or soft-tissue edema but are otherwise nonspecific. Although CT may be useful in defining the extent of soft-tissue involvement, MRI is the preferred modality. MRI may reveal extension of inflammation along the fascial plains.

Management

Emergent, wide surgical debridement is critical and may need to be repeated immediately [84,85,93]. Delays in surgery are associated with increased mortality, and antibiotic therapy in the absence of surgical debridement is ineffective [84,93]. Gram stain of surgical or aspirated material from the infected site may be helpful in guiding antibiotic selection. In patients with suspected GABHS infection, the antibiotic regimen should include intravenous penicillin (150,000 U/kg/d, divided every 4–6 hours) and clindamycin (40 mg/kg/d, divided every 6 hours).

Clindamycin is added for the “eagle effect,” which was first described in 1952 in a seminal article by Harry Eagle, MD, who described treatment failure of penicillin in mice injected with GABHS [82]. Eagle noted that “the greatly reduced therapeutic activity of penicillin in the older infections is due to the fact that the organisms are no longer metabolizing as actively as in the inflammatory focus.” In other words, GABHS initially proliferate rapidly until a steady state of growth is reached. Beta-lactam antibiotics are less effective during this steady-state phase, because they inhibit cell wall synthesis of actively replicating organisms. Clindamycin, however, is not affected by the decreased growth rate, because it works at the ribosomal level and offers the added benefit of reducing toxin synthesis by the organism [97]. The combination of a penicillin with clindamycin is more effective than either agent alone. In patients with polymicrobial infections, consider a beta-lactam/beta-lactamase inhibitor combination, such as ampicillin/sulbactam or piperacillin/tazobactam.

Supportive therapy includes careful fluid management, pain control, and management of multisystemic organ failure, usually in an intensive care setting. Patients with a GABHS necrotizing fasciitis are at risk for toxic shock syndrome, and many experts recommend intravenous immunoglobulin in this situation [98]. The role of hyperbaric oxygen therapy is controversial. Patients who survive may require amputation, skin grafting, and reconstructive surgery.

Summary

Musculoskeletal infections, including osteomyelitis, septic arthritis, necrotizing fasciitis, and pyomyositis, can occur in previously healthy children and lead to severe long-term morbidity if not recognized and treated promptly. Early diagnosis is crucial, and initial presentation is often to the primary care pediatrician. In addition to making a diagnosis, identification of the causative organism is imperative, especially in light of increasing resistance patterns. Identification may be accomplished through direct culture of debrided or aspirated tissue. Although they often produce negative results, blood cultures should be obtained in all cases because they may yield the pathogen. Initial antibiotic management should cover the most common etiologic organisms, and consideration should be given to local rates of community-acquired methicillin-resistant *S. aureus*.

Radiologic studies may be diagnostic, and the high sensitivity and resolution of MRI often make it the study of choice. In suspected cases of necrotizing fasciitis, prompt surgical management should not be delayed by radiologic evaluation. Although rarely fatal, musculoskeletal infections may be associated with long-term sequelae. Initial management should be aggressive, treatment courses should not be shortened, and long-term follow-up is essential.

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