

Osteomyelitis in Children

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Osteomyelitis is one of the more common invasive bacterial infections in children leading to hospitalization and prolonged antibiotic administration. Over the past decade, increasing microbial virulence, diminishing antibiotic sensitivity, and advances in diagnostic molecular microbiology and imaging techniques have led to changes in the clinical management of children with suspected osteomyelitis.

Pathogenesis

Most cases of osteomyelitis in children arise hematogenously, occurring characteristically in the metaphysis of long bones, such as the femur, tibia, and humerus [1]. Preceding blunt trauma to the site of the bone infection is quite common, but the role of trauma in the pathogenesis of osteomyelitis in children remains unclear [2]. Presumably, small hematomas in the metaphysis may permit microbial seeding after transient bacteremia. Penetrating injuries or surgical manipulation with such devices as spinal instrumentation are mechanisms for direct inoculation of bacteria into bone [3]. The least common pathway for osteomyelitis developing in children is local invasion from a contiguous focus of infection.

Microbiology

By far the most common bacterial pathogen causing osteomyelitis in children is *Staphylococcus aureus* in all age groups [1]. Some investigators have attributed the prominence of *S aureus* to virulence factors, such as the

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collagen adhesin encoded by the *cna* gene [4]. *S aureus* isolates from most children seen at Texas Children's Hospital with acute osteomyelitis, however, do not carry the *cna* gene [5]. Group A streptococcus (especially complicating varicella) [6], *Streptococcus pneumoniae* [7], and the emerging pathogen *Kingella kingae* [8] are the next most common organisms in infants and children. Group B streptococcus and gram-negative enterics are important agents in the neonatal period. *Salmonella* species are the most common cause of osteomyelitis in children with hemoglobinopathies [9] and *Pseudomonas aeruginosa* is particularly associated with puncture wounds of the calcaneus, metatarsal, and tarsal bones [10]. *Haemophilus influenzae* type b infection is now rare from the success of the *H influenzae* type b conjugate vaccine. In almost half of children with acute osteomyelitis, a bacterial etiology is never established [11]. Chronic osteomyelitis is most commonly caused by *S aureus* and gram-negative enterics. Polymicrobial etiologies are found in a high proportion of children with osteomyelitis secondary to trauma or infected contiguous soft tissue [12].

Clinical manifestations

The clinical manifestations of acute osteomyelitis in infants and children are well known and are not reviewed in depth in this article [1]. Osteomyelitis tends to be more diffuse in infants because of low anatomic barriers to limit spread of infection; concomitant septic arthritis, soft tissue infection, and pseudoparalysis of the involved extremity are common. In older children, infection is usually more focal. Fever and bacteremia are much more common in children with osteomyelitis than in adults.

Virulence of community-acquired methicillin-resistant Staphylococcus aureus

New manifestations of acute osteomyelitis are associated with clones of community-acquired methicillin-resistant *S aureus* (CA-MRSA) carrying the genes encoding Panton-Valentine leukocidin (*pvl*). Typically, only one site of infection is noted in children with acute hematogenous osteomyelitis caused by *S aureus*. Bocchini and coworkers [13], however, report that 15% of children with acute osteomyelitis caused by *pvl* + *S aureus* isolates have multiple sites of infection. In addition, myositis, pyomyositis, and intra-osseous or subperiosteal abscesses are more commonly seen in association with *pvl* + isolates than for *pvl*- isolates [12]. Up to 10 sites of bone infection have been seen with CA-MRSA isolates. Furthermore, chronic osteomyelitis is more likely to be present at the time of diagnosis or at follow-up with *pvl* + isolates than with *pvl*- isolates [14].

Severe life-threatening infections in adolescents in association with CA-MRSA osteomyelitis are also more frequent [15]. These patients with bacteremia and multiple sites of osteomyelitis quickly become severely ill

and require admission to the pediatric intensive care unit, most because of pulmonary involvement. Vascular complications, such as deep venous thromboses and septic pulmonary emboli, seem to be more common with CA-MRSA infections than was recognized in the past with *S aureus* osteomyelitis (Fig. 1) [14,16,17].

Pneumococcal and streptococcal disease

In a large series of children with pneumococcal bone infections from a multicenter study, the mean age of 21 children with bone infections was 12 ± 22.4 months [7]. Only four (19%) of the children had a history of antecedent trauma to the affected area. As with *S aureus*, the large bones were most commonly involved, but the calcaneus was infected in three, and the ileum or a rib in one each. Ten children with osteomyelitis of a long bone had septic arthritis of an adjacent joint.

In the most recent series of osteomyelitis caused by *Streptococcus pyogenes*, the mean age of the patients was 49.4 ± 38.7 months (range: 4–129 months) [6]. The mean ages of children with either *S pneumoniae* or *S pyogenes* osteomyelitis were younger than the age of children with *S aureus* osteomyelitis. As with *S pneumoniae*, osteomyelitis of cuboidal bones is more common with *S pyogenes* than with *S aureus*.

Vertebral osteomyelitis and diskitis

For vertebral osteomyelitis, the mean age in a series of 14 children was 7.5 years (range: 2–13 years), which was significantly older than the 36



Fig. 1. MR angiogram demonstrating occlusion of the popliteal vein behind the distal femur in adolescent boy with CA-MRSA osteomyelitis of the proximal tibia, complicated by deep venous thrombophlebitis.

children with diskitis (mean: 2.8 years; range: 7 months to 16 years) [18]. Preceding trauma was noted in only 2 of the 14 children. Back pain was the most common presenting complaint and the lumbosacral area was most commonly involved (64%), followed by the thoracolumbar area (29%). The mean duration of symptoms was 33 days (range: 5 days to 3 months).

Diagnosis

Laboratory investigations

When the history and physical examination suggest acute osteomyelitis, laboratory and diagnostic imaging evaluation are required to confirm the diagnosis. Standard laboratory indicators of inflammation, such as the total white blood cell count, erythrocyte sedimentation rate, and C-reactive protein, are all generally elevated. The C-reactive protein is most commonly increased, and was elevated in all (98%) but one of 44 children compared with an elevated erythrocyte sedimentation rate in 92% (35 of 38) in one series [19]. Both the erythrocyte sedimentation rate and the C-reactive protein at the initial evaluation, and the maximum value during hospitalization, were significantly higher in children with *pvl*+ *S aureus* isolates, compared with children with *pvl*- *S aureus* isolates [13]. Blood cultures are positive in 50% to 60% of patients [2,20]. Bone aspiration under CT or ultrasound guidance may reveal an etiologic agent when the blood cultures are negative [20].

Polymerase chain reaction may become an important diagnostic technique for determining the etiology of osteomyelitis when blood or bone cultures are negative. Polymerase chain reaction is already useful for cases caused by *Bartonella henselae* or *K kingae* [21]. Placing bone aspirates or synovial fluid into blood culture bottles enhances the yield of isolating *K kingae*, and may also serve as a medium for detecting 16S rRNA of *K kingae* by polymerase chain reaction.

Imaging studies

Plain radiographs early in the clinical course usually show soft tissue swelling and obliteration of tissue planes, but bone abnormalities, such as periosteal elevation or lytic lesions, are typically not identified until 10 to 14 days into the course. Plain films do help in demonstrating fractures or bone malignancies, which are included in the differential diagnosis of osteomyelitis. Technetium-labeled methylene diphosphate bone scan is about 90% sensitive in detecting osteomyelitis, and is especially useful if multifocal osteomyelitis is a concern, or the site of infection is poorly localized [22–24]. Periosteal abscesses can be detected readily by ultrasound, which is useful for helping to distinguish infection from infarction in bone of children with sickle cell disease [25].

MRI is now the most sensitive modality for detecting changes in bone consistent with acute osteomyelitis [24]. Bone marrow edema is seen as low signal intensity (dark) on T1-weighted images and high signal intensity (bright) on T2-weighted images (Fig. 2) [26]. Abscesses are best demonstrated with intravenous gadolinium contrast on the T1-weighted images with fat suppression. These changes are not specific, so findings must be interpreted within the clinical context [26]. In addition to bone abnormalities, myositis or pyomyositis contiguous to the site of osteomyelitis is readily detected. In the author's patients with *pvl* + *S aureus* isolates, 28 (62%) of 45 had surrounding myositis or pyomyositis on MRI, compared with 6 (31.6%) of 19 with *pvl*- isolates ($P = .05$) [13]. In addition, 34 (76%) of 45 of the group with *pvl* + isolates had subperiosteal or intraosseal abscesses, compared with 9 (47%) of 19 in the group with *pvl*- strains. MRI is especially useful for children with pelvic or vertebral osteomyelitis. Furthermore, MRI allows the orthopedic surgeon to plan the optimal surgical management for the patient. The disadvantages of MRI are the increased time required for scanning, the need for sedation in younger children, and the cost compared with CT.

Treatment

Empiric regimens for osteomyelitis in children

The selection of antibiotics for the empiric treatment of acute osteomyelitis in children should always include an agent directed against *S aureus*. Choosing a particular antistaphylococcal agent is now more complicated, however, in the era of CA-MRSA [27–29]. In the past, nafcillin



Fig. 2. Signal abnormality in the medial aspect of the distal right femoral metaphysis on the inversion recovery sequence of MRI of a child with CA-MRSA osteomyelitis.

or oxacillin had been the standard agent, or was included in a combination of antibiotics for empiric treatment. This is no longer appropriate where CA-MRSA isolates are common. In some regions of the United States, methicillin-resistant rates among community *S aureus* isolates are 75% or more [27]. Physicians must have some knowledge of the local rates of MRSA among community *S aureus* isolates, such as information derived from hospital or commercial laboratories processing *S aureus* isolates from local outpatients.

Some experts recommend that once the rate of methicillin-resistance among community *S aureus* isolates is $\geq 10\%$, antibiotics effective against CA-MRSA should be administered from the onset of treatment. Vancomycin is the gold standard for treating MRSA infections, and the addition of gentamicin, rifampin, or both for synergy may be helpful in children requiring intensive care unit admission. Recently, the value of adding rifampin to vancomycin for MRSA has been questioned [30]. In most areas of the country, 90% or more CA-MRSA isolates are susceptible to clindamycin. Clindamycin is an effective antibiotic for the treatment of acute osteomyelitis caused by CA-MRSA when the *S aureus* isolate is fully susceptible [15]. Microbiology laboratories, however, must screen for inducible macrolide-lincosamide-streptogramin resistance using the "D-test" [31]. Serious infections caused by *S aureus* isolates with inducible-clindamycin resistance should not be treated with clindamycin, because the risk of inducing resistance in vivo with resultant treatment failure is substantial [31,32]. When local clindamycin resistance rates among community *S aureus* isolates exceed 10% to 15%, clindamycin is not recommended for initial empiric treatment.

Vancomycin and clindamycin are also active against almost all isolates of *S pyogenes* and *S pneumoniae*, the other two main causes of acute hematogenous osteomyelitis in otherwise normal children [33,34]. Neither has in vitro activity against *K kingae*. In the normal child with osteomyelitis thought to have developed hematogenously, I prefer to initiate a single antibiotic. In our area with a very high rate of CA-MRSA, clindamycin or vancomycin is the agent of choice. Where CA-MRSA is unlikely, nafcillin or oxacillin is the agent of choice. If no organism is isolated and the child is clearly improving, a pathogen susceptible to clindamycin, vancomycin, or nafcillin is likely.

Oral step-down therapy

Once an organism is isolated and antibiotic susceptibilities are determined, antibiotic treatment may be modified. Nafcillin or oxacillin is the agent of choice for treating methicillin-susceptible *S aureus*. The main issues with prolonged nafcillin or oxacillin are the development of neutropenia related to bone marrow suppression, hypersensitivity reactions, and elevation in liver transaminases. Cephalexin or dicloxacillin are the primary oral antistaphylococcal β -lactam antibiotics used to complete therapy, after the patient has responded to a period of intravenous treatment [35–37].

Clindamycin is an excellent agent for treating methicillin-susceptible *S aureus* in patients allergic to or intolerant of nafcillin [38,39]. Clindamycin is also an important option for the treatment of CA-MRSA osteomyelitis caused by susceptible strains [14]. In either setting, clindamycin may be administered orally following appropriate intravenous treatment. Common adverse events with clindamycin are diarrhea and rash. Pseudomembranous enteritis secondary to *C difficile* toxin is the major concern with clindamycin, but this seems to be relatively uncommon in children even after prolonged administration [40].

Trimethoprim-sulfamethoxazole and tetracyclines

Other therapeutic options for CA-MRSA infections are less well studied for osteomyelitis. Virtually all CA-MRSA isolates are susceptible to trimethoprim-sulfamethoxazole, but there is little information on the use of trimethoprim-sulfamethoxazole in the treatment of invasive MRSA infections, especially osteomyelitis [41,42].

Long-acting tetracyclines, such as minocycline or doxycycline, have good in vitro activity against most CA-MRSA isolates. In a recent study, 24 adults with MRSA infections were treated with doxycycline or minocycline for greater than 50% of the total treatment duration [43]. Skin and soft tissue infections were the most common sites (67%), but four had osteomyelitis. Two of the four with osteomyelitis were considered cured. These investigators also reviewed the literature, and found four other patients with osteomyelitis treated with minocycline and rifampin. They concluded that doxycycline or minocycline might be reasonable oral alternatives for patients with skin and soft tissue MRSA infections, but that data are insufficient to recommend their routine use in osteomyelitis or bacteremia. Minocycline or doxycycline may only be considered in children over 8 years of age, because of the risk of stunted bone and tooth growth.

Linezolid

Linezolid is an oxazolidinone antibiotic, with excellent in vitro activity against MRSA isolates. It is approved for pediatric use. In a large comparative trial, linezolid was equivalent to vancomycin for the treatment of infections caused by resistant gram-positive bacteria [44]. In a subset analysis of children with MRSA infections in this and another trial of linezolid for skin and soft tissue infections, linezolid was effective for a variety of MRSA infections, including nosocomial pneumonia and bacteremia, but osteomyelitis was not included [45].

Although linezolid has not been evaluated in a formal manner for treatment of osteomyelitis, it has been used successfully in a compassionate use program [46]. Linezolid was administered to patients with multidrug-resistant gram-positive infections who were intolerant to other potentially

effective antibiotics, or who could not tolerate long-term intravenous antibiotic therapy. Fifty-five patients with a mean age of 58 years were evaluable for clinical assessment. Twenty-eight patients had long bone osteomyelitis. MRSA was the primary pathogen in 25 of 55 patients overall. At short-term follow-up a median of 21 days after the last dose, 16 (70%) of 23 patients with MRSA osteomyelitis were considered cured. Linezolid is an important oral agent for completing therapy for osteomyelitis caused by MRSA isolates resistant to clindamycin. Unfortunately, the suspension of linezolid is not very palatable for young children. Although linezolid is expensive, the oral route is convenient and cost effective, compared with home intravenous therapy with vancomycin.

The major side effects of linezolid are gastrointestinal disturbances, rashes, and elevated liver transaminases. A fall in hemoglobin or platelets may occur in adults receiving linezolid greater than 14 days [47]. In children, myelosuppression associated with linezolid is minimal in the first 2 weeks of therapy [48]. Long-term linezolid use in adults has been associated rarely with a peripheral neuropathy, and optic neuritis [49]. Lactic acidosis has also been reported in a few adults who received linezolid for prolonged periods [50].

Daptomycin

Daptomycin is a cyclic lipopeptide, with rapid bactericidal activity against MRSA in vitro [51]. Daptomycin is only available in an intravenous formulation. It is approved for the treatment of complicated skin and soft tissue infections in adults [52]. Daptomycin is inferior to ceftriaxone for the treatment of community-acquired pneumonia in adults, and currently is not approved for the treatment of pneumonia [51]. The lack of efficacy of daptomycin in pneumonia may relate to low concentrations of daptomycin in the bronchial-alveolar lining fluid and lung parenchyma, and inhibition of daptomycin by surfactant [51,53]. There are no pharmacokinetic data in children, so appropriate dosing for daptomycin in pediatrics is not known [54]. In addition, a substantial percentage of moderately ill children with *S aureus* osteomyelitis have pulmonary involvement, in which case daptomycin does not seem to be appropriate therapy as a single agent [55]. The role of daptomycin in the treatment of MRSA osteomyelitis in children is unclear.

β-Lactam antibiotics

Aqueous penicillin G is the agent of choice for treating osteomyelitis caused by group A streptococcus or penicillin-susceptible *S pneumoniae*. Amoxicillin or penicillin VK is the optimal agent for completing therapy with an oral agent. For pneumococcal isolates with resistance to penicillin, cefotaxime or ceftriaxone is recommended [7]. *K kingae* is susceptible to most β-lactam antibiotics, including nafcillin or oxacillin, and the second- and third-generation cephalosporins. Ceftazidime or antipseudomonal penicillins, plus an aminoglycoside, are typically administered for *Pseudo-*

monas osteochondritis. For *Salmonella* osteomyelitis, ampicillin is used for susceptible isolates. Cefotaxime or ceftriaxone are recommended for ampicillin-resistant isolates.

Antibiotics treatment is provided for a minimum of 21 days based on the study by Dich and coworkers [56]. I generally recommend treating until the C-reactive protein and erythrocyte sedimentation rate are both within a normal range, which typically requires 4 to 6 weeks of total therapy.

Surgical therapy

A drainage procedure is indicated if a subperiosteal or intraosseous abscess is present in patients with acute hematogenous osteomyelitis. This can often be accomplished through interventional radiology. Surgical debridement is more critical for optimal treatment of osteomyelitis associated with contiguous infections, direct inoculation, or chronic osteomyelitis [10,12]. Hyperbaric oxygen may be a useful adjunctive treatment measure in the management of chronic osteomyelitis that is refractory to standard approaches [57].

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