Osteoarticular Infections in Children

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KEYWORDS

• Pediatric • Osteoarticular infection • Acute bacterial osteomyelitis
• Acute bacterial arthritis • Septic arthritis • Hematogenous • C-reactive protein (CRP)

KEY POINTS

- Pediatric bone and joint infections peak at a rate of 80 per 100,000.
- Osteomyelitis and septic arthritis have a distinct profile of pathogens, age group affected, and duration of therapy, so consideration as separate entities is reasonable.
- Early diagnosis and treatment of osteoarticular infections is important to minimize complications.
- A thorough history and physical examination is critical to diagnose bone and joint infections.
- Laboratory evaluation should include, at a minimum, a complete blood count, blood culture, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP).
- Empiric therapy should target *Staphylococcus aureus* (methicillin susceptible and resistant) as the most common pathogen.
- Initial intravenous courses of antibiotic therapy are usually short: 3 to 7 days in most cases.
- Clinical examination, fever, and CRP dictate the duration of therapy and need for additional debridement surgery.

INTRODUCTION

Disease Description

Acute bacterial osteomyelitis (ABO) and acute bacterial arthritis (ABA) occur when a bacterial infection of the bone or joint occurs and are manifested most often by fever and pain or inability to use the affected limb. Although traumatic infections do occur,

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hematogenous ABA/ABO are much more common. The likely pathogenesis of acute hematogenous osteomyelitis in children is the simultaneous occurrence of occult bacteremia and an anatomic susceptibility to bacterial invasion of the well-vascularized metaphysis (most often of the long-bones) in children.[1–4] Between 15% and 50% of osteoarticular infections involved both the joint and the bone (**Fig. 1**).[5–7] Transphyseal vessels may allow direct invasion of the joint, and the joint may become infected as a result of infection of the adjacent metaphysis, which is intra-articular in young children.[7] These combined ABO + ABA infections tend to be more serious, with higher levels of inflammatory markers, more sequelae, and longer treatment courses.[5,7,8]

In 2015, the organisms for which a child is most likely to be bacteremic are also the most common organisms that cause ABO and ABA. Specifically, *S aureus*, methicillin susceptible (MSSA) and methicillin resistant (MRSA), have been the most commonly cultured organisms during the past 4 decades.[9,10] Before an effective vaccine, *Haemophilus influenzae*, type B, was the second most common cause of ABA,[10] although it is now rarely reported in well-immunized populations. *Kingella kingae* is an oral gram-negative bacterium, and descriptions of this fastidious organism causing ABO and ABA have been increasingly common because of better culture techniques, inoculating sterile body fluids into blood culture bottles, and advancing molecular techniques. A study suggested that by using molecular diagnostic methods, *K kingae* actually supplanted *S aureus* as the most common pathogen in ABO/ABA,[11] especially in children aged 1 to 2 years (**Fig. 2**). The list of pathogens is rounded out by less frequent but consistent isolation of *Streptococcus pyogenes, Streptococcus pneumoniae*, and even less commonly gram-negative enteric organisms such as *Salmonella* species and *Escherichia coli*. **Table 1** lists less common infections and possible exposures associated with them.

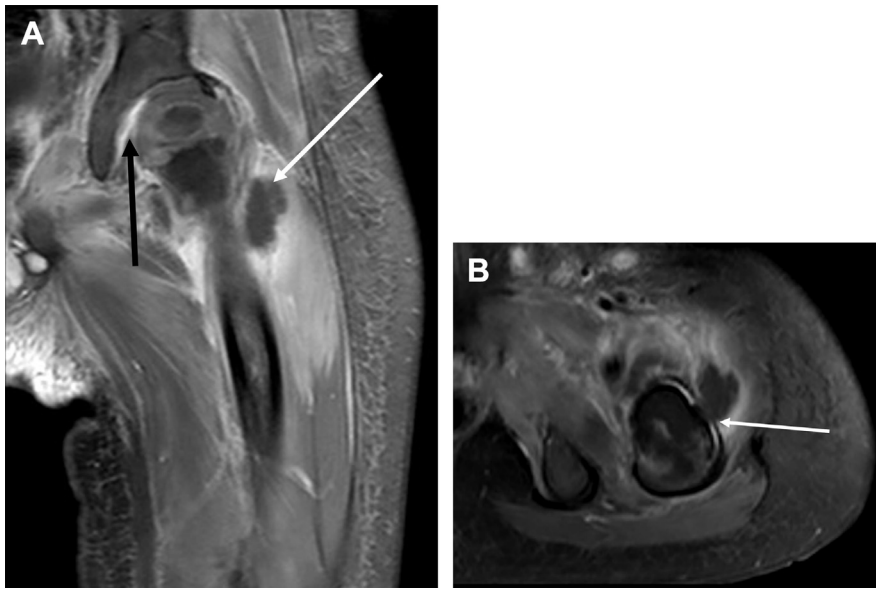

Fig. 1. (*A*) Coronal MRI of the hip. T1-weighted image of a child with osteomyelitis, arthritis (*black arrow* directed at joint effusion), and pyomyositis (*white arrow*) of the hip, caused by MRSA. (*B*) Axial MRI of the hip. T1-weighted image of the same child. In the axial image, the continuity of the proximal femur metaphysis and the adjacent abscess is appreciated (*white arrow*).

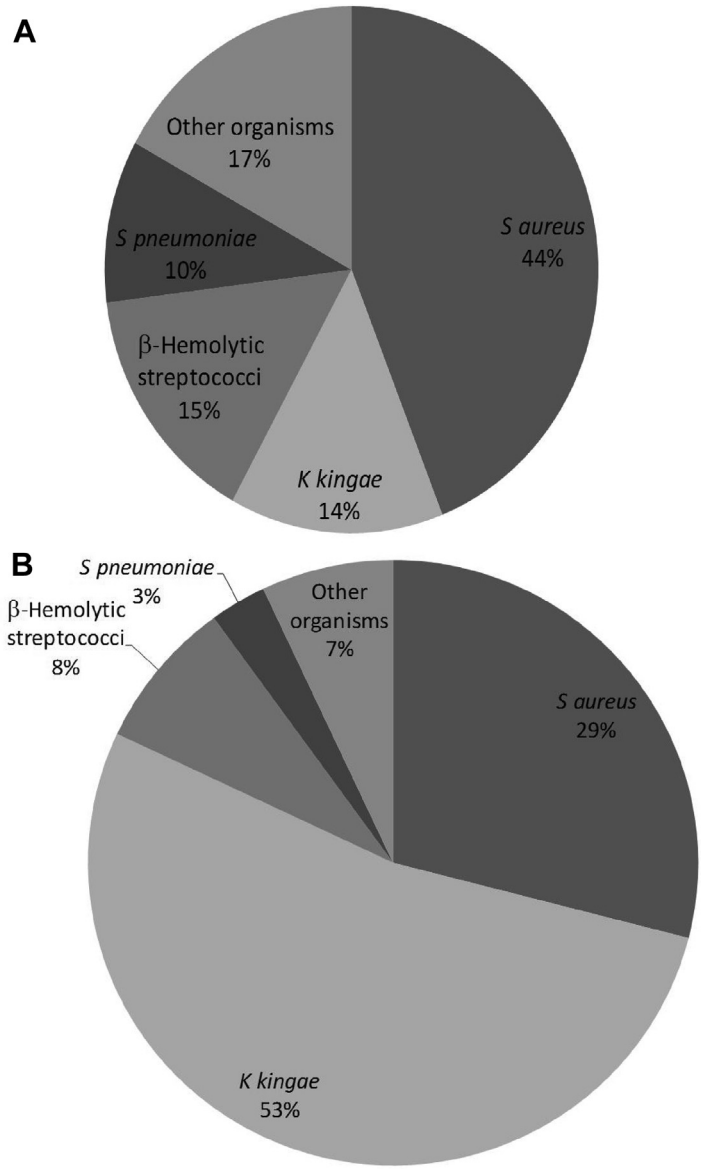

Fig. 2. Most common bacteria identified in osteoarticular infections either by (*A*) culture alone or (*B*) culture + polymerase chain reaction.

Prevalence/Incidence

- ABO and ABA occur worldwide and reflect the circulating microbial patterns and immunization rates.
- In well-resourced countries, the incidence of ABA is 4 to 10 per 100,000 children and ABO is estimated at 10 to 80 per 100,000 children.
- The incidence is higher in boys than in girls: a 2012 French study of 2592 children younger than 18 years with ABO or ABA had a male/female ratio of 1.4:1.[12]

Table 1
Important aspects of the patient history and associated pathogens or syndromes

Historical Finding	Associated Diagnosis
Travel	
International	Tuberculosis
Western United States	Coccidioidomycosis
Midwest United States	Histoplasmosis
Eastern United States	Lyme arthritis
Hunting/forest	Blastomycosis
Animal exposures	
Cat/kitten scratch	*Bartonella henselae*
Cat bite	*Pasteurella multocida*
Cat or livestock birth	*Coxiella burnetti* (Q-fever)
Reptiles/amphibians	*Salmonella* spp
Ingestions	
Unpasteurized dairy	Brucellosis Tuberculosis (*Mycobacteria tuberculosis*)
Not fully immunized	*Haemophilus influenza* *Streptococcus pneumoniae*
Sickle cell disease	*Salmonella* spp
Recent pharyngitis	*Streptococcus pyogenes* (invasive infection or postinfectious arthritis) *Fusobacterium necrophorum* (Lemierre disease)
Recent diarrheal illness	Postgastrointestinal infection arthritis (reactive arthritis) *Salmonella* spp

- Depending on the study, peak age of infection ranges from less than 2 years to 6 years, with isolated septic arthritis and *K kingae* infections occurring at younger ages, and osteomyelitis and *S aureus* occurring at older ages.[5,9,12–14]

Clinical correlation (**Fig. 3**) – Distribution of osteoarticular infections.[6,7,13–17] Overall, more than 80% of osteoarticular infections occur in the lower extremities.

Patient History

Most infections occur in the major weight-bearing joints or long bones of the extremities, for which the history most frequently encountered is that of a fever coinciding with the decreased use of the affected extremity. Older children may be able to identify the specific site of the infection; however, younger verbal children often simply say the extremity hurts. The diagnosis is even more challenging in nonverbal children. Fever and refusal to bear weight should be considered a lower extremity bacterial osteoarticular infection until proven otherwise.

Much more challenging is the vague history that occurs with the less common sites of osteoarticular infections, such as pelvic, sacroiliac, or vertebral infections. In these cases, there may be nonspecific discomfort or abdominal or flank pain, which is initially thought to be an intra-abdominal process.

Around 20% of children have a history of injury to the affected extremity or a nonspecific fall in the days or weeks before presentation; however, the frequency of falls and injuries in this age group is high, so the presence or lack of a history of falls should not affect the decision to consider an acute bacterial infection.[18]

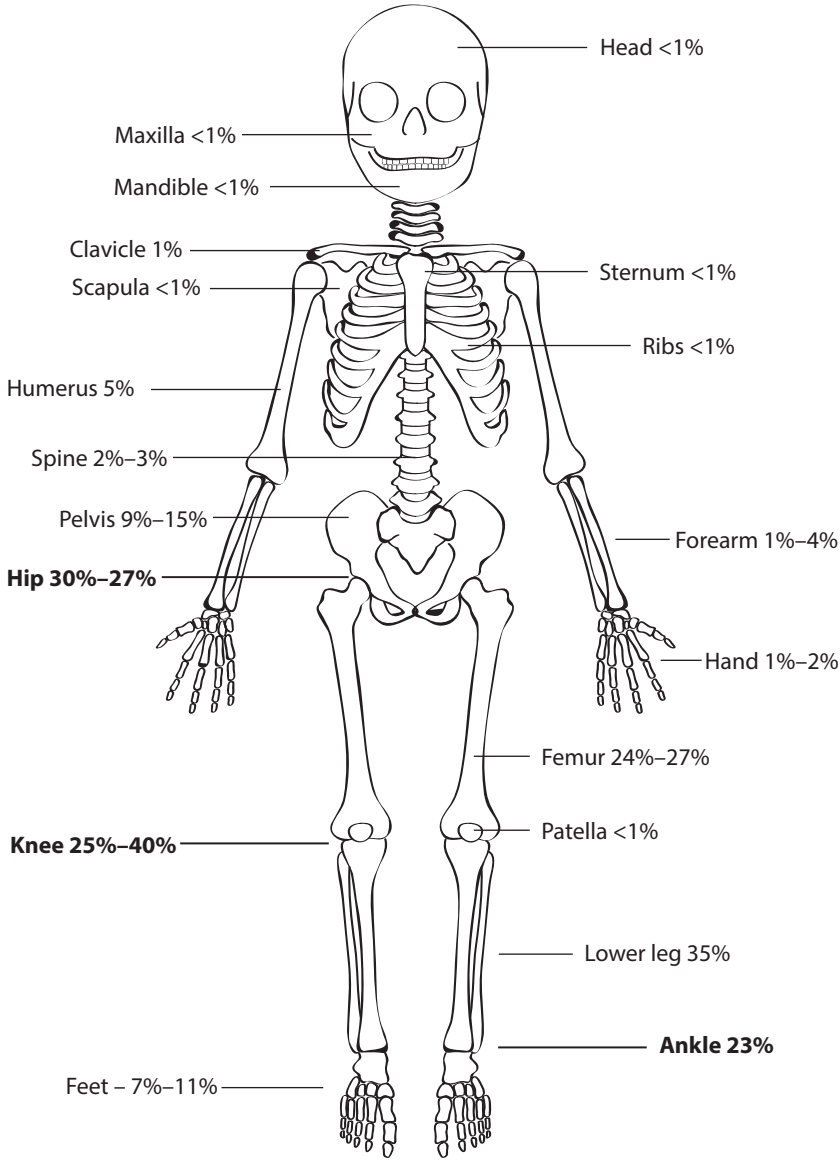

Fig. 3. Anatomic distribution of acute bacterial osteoarticular infections in children. Locations in bold face represent acute bacterial arthritis. All others represent acute bacterial osteomyelitis.

Supporting history is critical to ruling out uncommon infections (see **Table 1**). Travel history, sick contacts, and ingestion of unpasteurized dairy products should be queried to assess the risk of tuberculosis, brucellosis, and salmonellosis. *Bartonella henselae* and *Pasteurella multocida* infections are well described with exposure to cats and kittens.[19,20] The immunization status should be verified, especially when considering risk for *H influenzae* and pneumococcus. A family or medical history suggestive of sickle cell anemia or immunodeficiency could alter the empiric antibiotic

choices. The history of a recent pneumonia or persistent cough could suggest tuberculosis or dimorphic fungal infections, such as histoplasmosis, coccidioidomycosis, or blastomycosis.

Physical Examination

The physical examination of a child with suspected ABO or ABA can be a challenge. A wide range of clinical presentations exist based primarily on the pathogen and toxins that may be produced to create local or systemic disease (**Table 2**). A child with an acute osteoarticular infection may be well appearing with mild local tenderness or have an overwhelming sepsis syndrome. For uncomplicated ABO, there is often point tenderness at the metaphyseal site of infection, accompanied by warmth and swelling. The degree of pain, swelling, and tenderness depends on (1) the duration

Table 2
Pediatric osteoarticular infections: important aspects of the physical examination and associated pathogens or syndromes

System	Finding/Red Flag	Associated Diagnosis
Vital signs	Fever, tachycardia, tachypnea, hypotension	Sepsis
Appearance	Ill appearing, fussy, in pain	Sepsis, meningitis
Neck	Nuchal rigidity or neck stiffness	Meningitis, cervical or deep neck infection
	Adenopathy/swelling	Cervical or deep neck infection
Mucous membranes	Dry, tacky	Dehydration
	Erythematous	Staphylococcal/streptococcal toxin or Kawasaki disease
Eyes	Conjunctival injection	Staphylococcal/streptococcal toxin or Kawasaki disease
Heart	Murmur	Endocarditis
	Rub	Pericarditis from atypical organism (tuberculosis) or rheumatologic disorder
Lungs	Abnormal breath sounds, retractions	Associated pneumonia (especially *Staphylococcus aureus* or *Streptococcus pyogenes*) or adjacent rib infection
	—	Atypical infection such as tuberculosis, histoplasmosis, coccidioidomycosis, or blastomycosis
Abdomen	Pain, guarding	Pelvic osteomyelitis or nonosteoarticular infection (appendicitis, psoas abscess)
	Organomegaly	Atypical pathogen (*Brucella*, Q-fever) or non-infectious (rheumatologic or oncologic)
Musculoskeletal	Refusal to bear weight	Leg, pelvic, or vertebral infection
	Refusal to use extremity	Localized infection
	Hip flexed/externally rotated	Hip joint infection
	Pain/redness/swelling	Localized infection
Skin	Skin trauma	Traumatic infection or invasion of pathogen through the skin (*Streptococcus pyogenes* or *Staphylococcus aureus*)
	Diffuse rash	Staphylococcal/streptococcal toxin or Kawasaki disease
Neurologic	Weakness, abnormal reflexes	Spinal epidural abscess, transverse myelitis

of symptoms before presentation for medical evaluation, (2) the location of the infection, (3) the age of the child, and (4) the pathogen. Erosion through the cortex of the bone to create a subperiosteal abscess and subsequent rupture through the periosteum into the soft tissues of the extremity may lead to marked swelling and tenderness (see **Fig. 1**). With swelling and tenderness around a joint, it is not always possible to discern a primary osteomyelitis that has decompressed into the joint, from a primary joint infection.

It is important to assess vital signs to ensure the child is admitted to the appropriate unit. Tachycardia could be due to pain, fever, dehydration, or septic/toxic shock. Tachypnea may suggest a concomitant pneumonia. The child with a serious osteoarticular infection is often ill appearing, so examination for nuchal rigidity or other signs of central nervous system infection is important. A thorough examination includes auscultation of the heart for murmurs and the lungs for effusions or pneumonia. Palpation of the liver and spleen size could be important as clues for unusual infections as well as noninfectious causes of bone pain, such as lymphoma. A history of a chronic rash associated with joint pain could suggest a rheumatologic process.

The most important part of the musculoskeletal examination of a child with a suspected osteoarticular infection of an unknown location is to make the child comfortable. Generally, having the child sitting or lying on the mother's lap is recommended, so pain can be differentiated from the crying of fear or anxiety. Observation for reluctance to move an extremity or visible swelling can be helpful. Passive range of motion, starting with the unaffected extremities is a critical aspect of the examination. Palpation along the spine and gentle compression of the pelvis can help detect vertebral and pelvic infections.

A close examination of the skin and lymph nodes is needed to detect the redness, tenderness, warmth, and swelling associated with the primary infection, as well as adenopathy, rashes, abrasions, or scratches that might be important to the differential diagnosis. Assessment of the reflexes and strength is important to differentiate decreased movement of an extremity between osteoarticular infection and neurologic causes such as spinal epidural abscesses.

IMAGING AND ADDITIONAL TESTING

Laboratory Testing

The initial laboratory testing for a patient with suspected osteoarticular infection should, at a minimum, consist of complete blood count including a leukocyte differential, ESR, CRP, and a blood culture, with the culture obtained before antibiotic administration. In an analysis of 265 patients enrolled in a prospective study, the sensitivity of using elevated ESR and CRP level to diagnose acute osteoarticular infections was 98%.[8] Although validated only for ABA, in 1999, Kocher and colleagues[21] developed a clinical prediction scale that consisted of the following 4 criteria: fever, refusal to bear weight, leukocyte count greater than 12,000, and ESR greater than 40. The diagnostic sensitivity for ABO was 93% and 99%, respectively, for the presence of 3 or 4 criteria. A blood culture is recommended because of the presence of bacteremia in as many as 59% of patients.[22] Additional testing, such as serologic testing for various pathogens (eg, *Bartonella*, *Histoplasma*, or *Brucella* antibody), tuberculin skin testing, or an interferon-gamma release assay test for tuberculosis, may be useful depending on the clinical scenario. The need for a stool culture would be determined by risk factors in the patient's history. If surgical specimens are obtained, they should be submitted for bacterial, fungal, and mycobacterial cultures

and staining, and joint fluid should be inoculated into a blood culture bottle to enhance the growth of fastidious organisms.

The future of testing for osteoarticular infections may include several methodologies that are either recently available or currently in the testing phases. Molecular detection of nucleic acid using pathogen-directed (*S aureus*) or broad bacterial (16S ribosomal DNA) polymerase chain reaction methodology will likely become a mainstay at many larger institutions, because of rapid turnaround times and the ability to detect pathogens in cases in which cultures are negative.[23,24] Table-top devices designed to analyze finger-stick blood samples for CRP are commercially available but are not used at most institutions currently. Newer tests that are nonspecific for inflammation are more sensitive in detecting inflammation from a bacterial infection earlier in the disease process. One such marker is procalcitonin, which has been studied for ABO and ABA and found to be sensitive[25]; however, it is not yet available at this time to most clinicians in the United States.

Radiologic Imaging

Although a conventional radiograph of the affected site is certainly recommended in all cases, its sensitivity in acute infection is extremely low because 50% bone mineral loss must occur to see an abnormality[26] and abnormalities usually appear 10 or more days after the onset of the infection. A radiograph is important to exclude other processes such as an acute fracture.

MRI is the mainstay of imaging methodologies for suspected osteoarticular infections when an anatomic site is identifiable. MRI is sensitive in detecting cortical and bone marrow edema and inflammation. It is occasionally difficult to differentiate a bone infection from adjacent soft-tissue infection creating sympathetic edema in the bone. The major advantage of MRI is that it provides high-quality images of the bone, joint, and surrounding tissue, which is critical to guide the decision on whether surgery might be necessary for a subperiosteal abscess or associated pyomyositis.

Bone scans have been used for decades and consist of injection of a radiotracer (usually technetium 99) followed by a series of images immediately after and hours after injection. The tracer is retained in areas of increased blood flow, and the presence of increased tracer (or in some cases absent tracer where it is expected) is considered abnormal. Although the bone scan is sensitive for osteoarticular infections,[27,28] it generally gives abnormal results in bone-related cancers and fractures and is more difficult to interpret in children because of normal uptake into the growth plate. Despite these complicating issues, bone scan remains an important test when multifocal disease is suspected, when osteoarticular disease of an unknown anatomic site is suspected, and when MRI is not readily available. Bone scans also have the advantage of lower cost and less often requires anesthesia for young children, and the radiation risk is considered very low.

Ultrasound imaging of suspected joint infections is a rapid, noninvasive test with no radiation risk and is particularly helpful for suspected hip infections in which case palpation is not sensitive to detect effusions and rapid drainage of the joint is often desired. Although a negative result on ultrasound imaging of the hip is sensitive and the absence of fluid in the hip generally rules out a septic arthritis,[29] similar symptoms can be caused by a nearby osteomyelitis or pyogenic myositis. Therefore, a negative result on ultrasound imaging may need to be followed by an MRI if symptoms are severe or persistent.

The most practical approach to imaging, then, is to obtain a plain radiograph and an ultrasound image for suspected deep joint infections and then proceed to MRI, based

on the presentation, focal examination findings (or lack thereof), and availability of the technology and sedation capabilities. For the ill-appearing child, because of the high probability of bacteremia, therapy should not usually be withheld while awaiting imaging and/or surgery, especially if the child demonstrates any signs or symptoms consistent with sepsis.

SURGICAL TREATMENT

Although the initial choices of antimicrobials are discussed later, one of the first questions to be answered when treating a child with an osteoarticular infection is "does the child need surgery?" There are 3 basic reasons for surgical intervention in ABA and ABO: microbiologic diagnosis, source control, and preservation of maximal function. As with many areas of bone and joint infections, there are few studies on which to make an evidence-based decision.

Starting with preservation of function, it has often been assumed that lack of drainage or delayed drainage of a major joint such as the hip would increase the chance of complications such as avascular necrosis or permanent cartilaginous damage. Limited data are available to support this conclusion, in part because many physicians have been uncomfortable studying immediate versus delayed incision and drainage of the hip. Immediate drainage and irrigation of all major joints (eg, hips and shoulders) suspected of having a bacterial infection is still considered the standard of care in many settings. A 2009 publication describing a series of prospectively enrolled children in Finland with ABA reported good outcomes, with 84% having needle aspiration of the joint and only 12% undergoing a full arthrotomy; none of the children had MRSA infection.[15] Given that surgical treatment was at the discretion of the physician, the benefit of surgery in more severe cases still cannot be excluded.

Source control is probably one of the most important reasons for surgical intervention. In the 30% to 56% of patients with bacteremia, drainage of the source is important, especially with persistent bacteremia. Furthermore, in the case of subperiosteal abscess, the effective antimicrobial therapy requires the drug to reach the source of the infection and the success of early therapy largely depends on removal of purulent fluid, debridement of necrotic tissue, and restoration of blood flow to the site. Based on published experience, one of the most important indicators of adequate source control is a sustained and rapid decrease in the CRP level.[5] For cases in which the CRP level does not decrease within the first 48 hours or initially decreases and then plateaus more than 5, an undrained, persistent purulent collection requiring surgery or possibly an occult sequestered focus initially missed by history, examination, or imaging is likely.[5,30]

Finally, confirmation of a pathogen is critical to selecting the best, most narrow-spectrum antimicrobial for definitive therapy. National guidelines being written for the diagnosis and management of pediatric bone and joint infections, cosponsored by the Pediatric Infectious Diseases Society and Infectious Diseases Society of America, stress the importance of cultures when an orthopedic surgeon decides to aspirate or formally open the suspected site of infection (Bradley, personal communication, 2015). However, wide variation in the surgical approach exists in North America with respect to indications for bone aspiration and formal debridement, including the creation of a bone window for ongoing drainage following the procedure. However, for mild or moderate infections involving the midshaft of a long bone, and without evidence of an abscess, some experts believe that the risks of surgery may outweigh the benefits. Using objective measures such as the CRP level to trend the success of

therapy can be helpful in reassessing the need for surgical intervention. Having a good working relationship between medical and surgical care providers is critical to making the right risk to benefit decision.

MEDICAL TREATMENT

Antibiotic Choice

The decision of which antibiotic to use empirically and as definitive therapy has also been an area of debate, especially since the early 2000s with the emergence of community-associated (CA)-MRSA. Based on the historical pathogens, the mainstay of therapy until the emergence of MRSA was β-lactams, including the first-generation cephalosporins (cefazolin/cephalexin) and the penicillinase-stable penicillins (dicloxacillin and oxacillin). *K kingae* is also susceptible to first-generation cephalosporins and oxacillin (with resistance to clindamycin and vancomycin). Therefore, these early empiric treatment regimens, before the introduction of CA-MRSA, addressed all the top pathogens even when cultures could not be obtained or were negative. When an organism is identified and is known to be susceptible, β-lactam antibiotics are still the preferred therapy for osteoarticular infections.

However, as CA-MRSA emerged and became a significant contributor to osteoarticular infections, the empiric and definitive therapy strategies had to be adjusted. The obvious first choice of therapy was the glycopeptide vancomycin, for which resistance in *S aureus* continues to be extremely unusual and there is no resistance among group A streptococcus or *S pneumoniae*. Although the advantage of vancomycin is the likelihood that any of the gram-positive pathogens will be adequately treated, there are disadvantages that must be considered when using this antimicrobial for the initial treatment of bone and joint infections. The first and foremost is that vancomycin has no activity against the potential gram-negative organisms that can cause osteoarticular infections. In a highly immunized population, *K kingae* is the leading gram-negative pathogen, but based on immunization status and other risk factors, consideration might be given to *H influenzae* and *Salmonella* species. A second consideration is the decreased effectiveness of vancomycin in comparison with the β-lactam class when treating otherwise susceptible *S aureus*. Multiple investigators have described worse outcomes when vancomycin monotherapy is used in place of β-lactams for a β-lactam–susceptible organism. One such example was a 37% versus 18% mortality in patients with MSSA bacteremia treated with vancomycin or a β-lactam, respectively.[31] Finally, vancomycin is a medication that can be given only intravenously (IV) and must have blood level monitoring to minimize toxicity and maximize effectiveness, particularly with the higher dosages that seem to be needed to treat invasive CA-MRSA infections.

One of the most common alternative therapies is clindamycin, which has a successful record in the treatment of ABA and ABO. Clindamycin belongs to the lincosamide class and is a protein synthesis inhibitor that has traditionally been used as an alternative for gram-positive organisms causing bone and joint infections in a patient allergic to β-lactam or when the organism is resistant to first-line β-lactam therapy. Several studies have documented effectiveness in osteoarticular infections, including prospective, comparative evaluations.[32,33] The emergence of CA-MRSA across the country has highlighted the weakness of clindamycin, which is resistance. Resistance to clindamycin is variable, ranging from 7% to 50% among CA-MRSA.[34,35] The *erm* gene encodes the methylase protein that is responsible for methylation of the 23S rRNA-binding site, ultimately causing resistance to clindamycin as well as macrolides and streptogramins (dalfopristin/quinopristin), and is referred to as the MLS-B

(macrolide, lincosamide, streptogramin-B) mechanism.[36] This methylase may be inducible or, in a subset of any population of *S aureus* that contain the gene, be constitutively producing the enzyme such that this subpopulation of organisms is always resistant to clindamycin, even before exposure. This subpopulation is likely to be selected during therapy with clindamycin, leading to treatment failure in high-density infections. The microbiological manifestation of inducible MLS-B (iMLS-B) is demonstrated by the induction of clindamycin resistance in the presence of erythromycin, which approximates a D instead of a perfect circle and is thus called the D-test (Fig. 4). In addition to selection of constitutive methylase-producing organisms, there is clinical concern for induction of the *erm* resistance while on therapy, so most treatment guidelines suggest that clinicians avoid the use of clindamycin altogether with D-test-positive organisms. However, there have only been rare reports of actual treatment failure and the development of resistance on therapy,[36–38] and many patients have undoubtedly been successfully treated with clindamycin despite having an inducible MLS-B genotype pathogen. There are few data to inform on whether it is reasonable to use clindamycin for a D-test-positive organism in mild skin and skin structure infections (SSTI) or for convalescent therapy in mild osteoarticular infections. Logic would suggest that for a mild, low-density infection or for an infection in which good source control has occurred, and is responding to therapy, it could be appropriate to continue therapy with clindamycin despite the presence of a positive result on D-test, avoiding the need to use more toxic or less well-studied antibiotics. An important and often overlooked detail is that clindamycin resistance among group

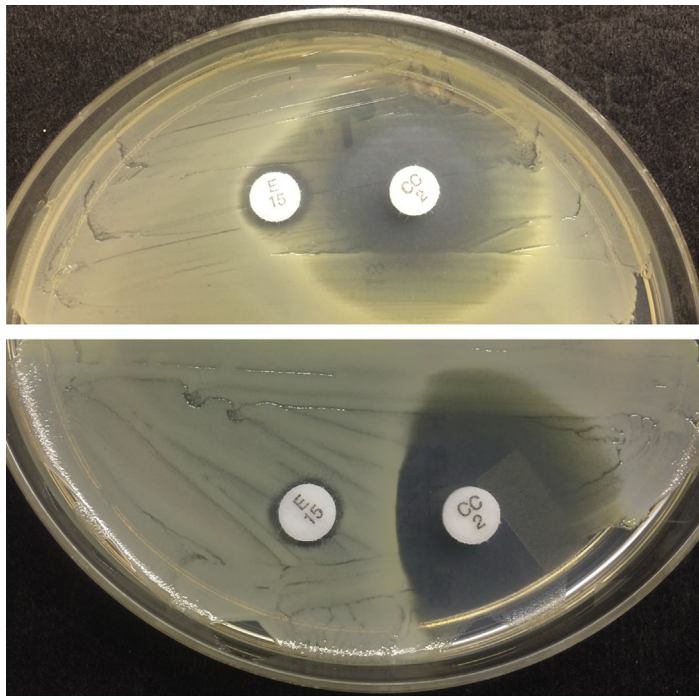

Fig. 4. The D-test result is determined by the pattern of growth when an erythromycin and clindamycin disc are placed in proximity. D-test negative (*top*) indicates no inducible clindamycin resistance. D-test positive (*bottom*), which approximates the shape of the letter D indicates inducible clindamycin resistance.

A streptococcus is around 15% in many communities and inducible MLS-B resistance was described in the 1980s in *S pyogenes*,[39] so it is not exclusively present in *S aureus*. In the right setting (ie, organism that is not susceptible to β-lactams or in a penicillin-allergic patient), clindamycin is still a mainstay of oral therapy for osteoarticular infections. The main limitations of clindamycin are diarrhea (including a low rate of *Clostridium difficile* enteritis) and poor compliance for children to take it, given the unpalatable taste of the suspension.

With the dramatic increase in CA-MRSA, trimethoprim-sulfamethoxasole (TMP-SMX, Septra, Bactrim), has come into favor in the treatment of skin and skin structure infections and to some extent osteoarticular infections. TMP-SMX, with a mechanism of action of inhibiting 2 different steps in intrinsic folic acid synthesis, has a history as an effective antimicrobial mainly in the treatment of gram-negative organisms such as the common causes of urinary tract infections. Initial enthusiasm as an effective therapy for respiratory tract infections caused by gram-positive organisms quickly faded as it became clear that resistance developed rapidly in streptococci. However, CA-MRSA is generally susceptible to TMP-SMX, so a resurgence of its use has occurred, especially for SSTI, for which data support its general effectiveness.[40] Although use of TMP-SMX in ABO/ABA has increased, there are no high-quality retrospective studies evaluating its outcomes in bone or joint infections caused by CA-MRSA or prospective comparisons with any of the other traditional antimicrobials in osteoarticular infections. Conversely, there have been no reports of treatment failures with sulfonamide therapy, so the use of this class might be considered, especially where clindamycin is not an appropriate alternative. The main concerns with TMP-SMX are the rare side effects of temporary bone marrow suppression and Stevens-Johnson syndrome.

The last 2 decades have established a place for linezolid in the treatment of bone and joint infections. The oxazolidinone shares a similar mechanism of action (ribosomal protein synthesis inhibition) with clindamycin, although it has a broader spectrum of activity among gram-positive organisms. Well-designed studies established appropriate dosing for neonates, infants, and children early following its approval in the United States, and the anecdotal successful use of linezolid for ABA and ABO has been described.[41] One major advantage of linezolid is the almost 100% gastrointestinal absorption compared with IV dosing. However, cost remains prohibitively high to recommend its frequent use and serious side effects include thrombocytopenia and neutropenia occurring after 10 or more days of use.

Other alternatives that are less frequently used because of either age limitations or lack of data on dosing or effectiveness include doxycycline, fluoroquinolones, and daptomycin. The addition of rifampin for certain infections such as bloodstream infections and device-related infections is occasionally recommended[42] but there are no published data to support routine use of rifampin combination therapy in pediatric osteoarticular infections. Daptomycin is currently being investigated in a prospective comparative trial for ABO, as documented on ClinicalTrials.gov (NCT01922011). Other glycolipopeptides and oxazolidinones may be studied for pediatric osteoarticular infections in the future.

Given all of the presented information on the pros and cons of different antimicrobials, there are several different strategies used in the empiric and definitive choice of antibiotic therapy for bone and joint infections. Some of the decisions are dictated by the clinical presentation and others by local resistance patterns. For example, a critically ill child with a suspected osteoarticular source would be likely to have *S aureus* or *S pyogenes*. Therefore, the combination of vancomycin and a broad-spectrum β-lactam would be appropriate with the possible addition of clindamycin if toxic shock is suspected (based on the ability of clindamycin to decrease ribosomal production of bacterial toxins). A similar combination might be considered for an

obvious septic arthritis of the hip, in which preserving maximal function is paramount. On the other hand, for the nontoxic child with a bone or joint infection in regions where the resistance to clindamycin is 10% or less, empiric clindamycin therapy with close observation is reasonable, given the greater safety of clindamycin compared with vancomycin. No prospective data for TMP-SMX monotherapy of bone or joint infection exist; therefore, use of the TMP-SMX should be reserved for children for whom well-established antibiotic options are not available.

The final consideration is whether *K kingae* should be treated empirically. Some clinicians ensure that adequate gram-negative therapy is initiated for all patients, whereas others would be comfortable with initial therapy targeting gram-positive organisms (eg, clindamycin or vancomycin) and adding therapy for *K kingae* if resolution is not rapid (within 48–72 hours, particularly in situations in which cultures are negative). There is some aspect of the art of medicine when choosing antimicrobial therapy for the treatment of ABA and ABO.

Route and Duration of Therapy

The route and duration of treatment of osteoarticular infections has been an area of debate for decades. Until the 1980s, the best treatment route and duration was thought to be long intravenous courses of antimicrobials to prevent a relapse or complications. Outpatient intravenous antibiotic therapy was not feasible at that time, and therefore, children with bone and joint infections were required to spend 4 to 6 weeks in the hospital while receiving therapy. Thirty-five years ago, it was suggested that a transition to oral therapy could be safe and equally effective. Syrogiannopoulos and Nelson[10] published data that described the duration of IV and oral antimicrobial therapy and the outcomes and found that combined courses of IV and oral therapy were safe and effective in the range of 4 to 6 weeks. However, the initial duration of IV therapy was not precisely defined, and for decades to follow the original dogma of long IV courses of therapy remained the rule for many physicians. Recent reviews on route of therapy, based on retrospective review of national pediatric hospital databases, have documented that transition to oral therapy produces equivalent outcomes, with fewer therapy-associated adverse events.[43,44] However, the factors involved in considerations for time to switch to oral therapy and the duration of therapy have not been well addressed.

In the past 2 decades, there has been a keen interest in minimizing the duration of antimicrobial therapy. Reasons for this include health care costs, antimicrobial resistance, nosocomial infections and other hospital-related risks, risks of central venous access, and most importantly patient comfort and lifestyle.

In 2012, Arnold and colleagues[5] published an article describing 194 patients who had ABO, ABA, or both. During the 7-year review period, the group of Pediatric Infectious Diseases and Pediatric Orthopedic Physicians used a strategy of transitioning to oral therapy when the patient was afebrile, able to use the affected extremity with minimal pain, and the CRP level was less than 3 μg/dL. The care of 113 patients with ABO, 32 patients with ABA, and 49 with both was reviewed. This study described a total IV duration of 1.4 weeks for ABO and ABA and 2.7 weeks for ABO + ABA, with variability by the pathogen, whereby the duration of IV therapy tended to be longer for MRSA and much shorter for *S pneumoniae*. The total duration of therapy was 7.3 weeks for ABO, 4.7 weeks for ABA, and 7.9 weeks for ABO + ABA. The most important point from this article, however, is that using the strategy of transitioning to oral therapy when the 3 criteria are met (CRP<3, afebrile, and decreased pain), only 1 of 194 patients had a treatment failure, and this was thought to be due to a retained infected bone fragment in the hip joint where the initial infection occurred. In addition, those patients

who were defined as having a complicated course actually had a lower CRP level at the transition to oral therapy than those who had an uncomplicated course, which implied that the physicians had an understanding of the more serious nature of that specific infection, so more conservative criteria were used to decide when oral therapy could be started. Therefore, as opposed to setting a standard duration of IV and oral therapy, this 2012 article suggests that using subjective and objective findings, including CRP level less than 3, patients may safely be switched to oral therapy.

A 2013 publication by Copley and colleagues[45] described the impact of implementation of a clinical guideline that standardized diagnosis and treatment of osteomyelitis at their hospital. The duration of therapy was based on the clinical response and CRP level, for which a CRP level of less than 2 mg/L was considered one of the criteria for switching over to oral therapy and discharging home. In a preintervention and postintervention retrospective design, the records of 210 children were reviewed. Although no specific complications were mentioned, the readmission rate was 11.4% for the preguideline cohort and 6.6% in the postguideline cohort ($P = .34$). The preguideline cohort also had a longer length of stay (12.8 vs 9.7 days, $P = .54$).

A series of articles have also been published by Peltola and colleagues[15] which advocate for an even earlier switch to oral antimicrobial therapy and shorter total durations.[16,46–49] These publications have focused on a multisite cohort of children who were enrolled in a series of prospective studies that began in 1983. The first publication in 1997 included 50 patients infected with *S aureus* (all MSSA) who were treated IV for an average of 4 days, with a total duration of IV + oral therapy of 3 weeks.[49] No adverse outcomes were reported at a 12-month follow-up, and it was suggested that shorter treatment durations were safe and effective. Following this initial publication, children with ABA were enrolled and randomized to either a first-generation cephalosporin (which changed during the course of the study) or clindamycin for a total duration of 10 or 30 days, and those with ABO were randomized to the same antimicrobials for a duration of 20 or 30 days.[15,16] The IV course was generally 2 to 4 days, followed by oral medication; however, treating physician discretion allowed for protocol deviation and prolongation of either IV or oral antimicrobial therapy. The outcomes of shorter-course therapy were overall favorable, with only 1 of 235 patients reported to have truly failed shorter-duration therapy; a 10-year old boy had 2 separate recurrences (one with the original *S aureus* and the other with a coagulase-negative staphylococcus) in the same location as the original infection. This patient was in the longer-course group at randomization. Some caution must be used when generalizing these results. First, particularly for the ABA series, 17% of the patients had *H influenzae* type B, and of the *S aureus*, all were MSSA, so it is unclear whether in an era when 50% or more of the invasive isolates are CA-MRSA, the same short-course therapy would be as successful. In addition, 7% of the ABA and 5% of the ABO cases deviated from the short-course therapy for either slow clinical response or a persistently elevated CRP level. Therefore, a single short-course protocol should be adopted with caution and should never override the clinical judgment if a slow response is observed.

Using the information detailed earlier, it is reasonable to presume that a shorter course of IV therapy followed by oral therapy is safe and effective for most patients with hematogenous osteoarticular infections. Using objective measures to guide the duration of therapy is the more conservative route but will still lead to short IV courses. There are data to support shorter oral courses of therapy as well, although in an era of frequent CA-MRSA infections more data may be needed to adopt this universally, and clinical judgment is always an important aspect when deciding the duration of therapy.

Complications and Concerns

Although antimicrobial therapy is now successful in achieving a complete cure for most patients, there are still adverse outcomes related to severe disease, delayed therapy, and the location of the infection. The most severe outcome would be death due to the infection, which most often is related to sepsis from the initial infection. In environments of easily accessed and early medical care, death as a complication of osteomyelitis is rare, with no deaths in any of the large series described earlier. Persistent bacteremia without sepsis is most likely due to an undrained abscess, a septic thrombophlebitis adjacent to the infection, or, rarely, an associated bacterial endocarditis. MRSA osteomyelitis in particular has been associated with deep venous thrombosis and infected pulmonary emboli.[50,51]

Less serious but more frequent are the complications related to the site of infection. For example, with infections frequently occurring at the end of the long bones, damage to the growth plate with subsequent growth plate arrest and limb length discrepancy is a common concern. Similarly, femoral head damage with resultant avascular necrosis is a rare complication. However, each of these complications was only documented in 0% and 2% of the modern era studies discussed earlier.[5,15] Similarly, pathologic fractures and loss of function may rarely occur in any weight-bearing locations, such as the vertebral body.

Relapse of infection is also extremely uncommon with current therapeutic strategies, with only 1 relapse in each of the large series described previously. Chronic osteomyelitis, a common complication in the preantibiotic era, is virtually unknown with present management strategies.

SUMMARY

Pediatric hematogenous osteoarticular infections are uncommon, although given the consequences of a missed or late diagnosis, providers of pediatric acute care should be familiar with the presentation, diagnosis, and initial therapy. The history of fever and refusal to walk or use an extremity should prompt an immediate evaluation for a bacterial bone or joint infection. A thorough history and physical examination can help to diagnose less common pathogens and identify the site of infection for difficult-to-localize regions such as the spine or pelvis. Laboratory evaluation should include a complete blood count, blood culture, and markers of inflammation (ESR and CRP). Initial empiric therapy should include agents active against *S aureus* (including CA-MRSA), streptococci, and ideally *K kingae*. Although a short IV course with a rapid transition to oral therapy is now the rule for an uncomplicated case, the ideal time to switch to oral therapy, the total duration of therapy, and the need for surgery are still in need of systematic, prospective study and should be individualized based on the patient.

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