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Management of acute hematogenous osteomyelitis in children

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Abstract

In children, osteomyelitis is primarily hematogenous in origin and acute in nature. The principal cause of osteomyelitis in children is *Staphylococcus aureus*, and both the epidemiology and pathogenesis of *S. aureus* infections, including osteomyelitis, have changed in recent years owing to the emergence of community-associated methicillin-resistant *S. aureus*. This review focuses on advances in the diagnosis and overall management of acute hematogenous osteomyelitis in children with these changes in mind.

Keywords

acute hematogenous osteomyelitis; AHO; antibiotic therapy; CA-MRSA; children; community-acquired methicillin-resistant *Staphylococcus aureus*; diagnostic imaging; osteomyelitis; *Staphylococcus aureus*

Osteomyelitis is strictly defined as any form of inflammation involving bone and/or bone marrow, but it is almost exclusively the result of infection. It is a complicated infection that takes diverse forms, particularly from the point of view of the most appropriate therapeutic approach to use, and for this reason several classification schemes have been used to describe osteomyelitis. One of these focuses on the source of the infection and distinguishes between infections arising from hematogenous seeding from the endosteal blood supply and infections arising as a consequence of an overlying soft tissue infection (osteomyelitis secondary to a contiguous focus of infection) and/or vascular insufficiency [1]. A second scheme that applies irrespective of the underlying source of the offending bacterium distinguishes between acute, subacute and chronic infection based on the time between the onset of symptoms and diagnosis [1].

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Acute osteomyelitis is defined as an infection diagnosed within 2 weeks of the onset of symptoms [1,2]. Subacute osteomyelitis is diagnosed 2 weeks after the onset of symptoms, and chronic osteomyelitis months after the onset of symptoms [2]. While there are no studies that we are aware of that specifically address the issue, we believe that this time frame must be dependent, at least to some degree, on the virulence properties of the infecting strain. *Staphylococcus aureus* is the predominant pathogen responsible for osteomyelitis in children (see later), and it is possible that the time frame of infection may change in children infected with community-associated methicillin-resistant *S. aureus* (CA-MRSA), many strains of which are hyper-virulent for reasons that have yet to be fully explained [3]. If so, this would create an urgent need for the development of diagnostic methods capable of detecting infection in its early stages.

Both of the classification schemes cited previously are relevant to this discussion in that, unlike the infection in adults, osteomyelitis in children is generally of hematogenous origin and is most often acute [1,2,4]. A primary contributing factor, with respect to the prevalence of the hematogenous route of infection, is the nature of the endosteal blood supply in the growing bones of children [1,2,4].

Neither of these distinctions is absolute in that osteomyelitis in children may be caused by local extension from a contiguous soft tissue infection or, more rarely, by direct inoculation of the offending pathogen into the bone. Chronic infections do occur in children, generally as a consequence of failed antimicrobial therapy or the presence of an orthopedic implant. Chronic infection is additionally defined by the formation of a sequestrum of dead bone, and successful resolution of such infections usually requires surgical debridement and prolonged antimicrobial treatment, the latter sometimes taking the form of both systemic and local antibiotic delivery [1]. While both of these issues are addressed in this review, given its predominance among children, the primary focus is on the diagnosis and management of acute hematogenous osteomyelitis (AHO) in the pediatric patient.

Microbial etiology of acute hematogenous osteomyelitis

Acute hematogenous osteomyelitis typically arises in the metaphysis of long tubular bones, with approximately two-thirds of all cases involving the femur, tibia or humerus [1,2,4]. While a variety of bacterial pathogens may be involved, *S. aureus* is the pre-eminent pathogen and is responsible for 70–90% of AHO infections in children [2,4]. Other etiological agents, in no particular order, include *Streptococcus pyogenes*, *Streptococcus pneumoniae*, Group B streptococci (in infants), coagulase-negative staphylococci (especially in implant-associated infections), *Kingella kingae*, enteric Gram-negative bacilli (especially *Salmonella* spp. in individuals with sickle cell disease) and anaerobic bacteria. *Haemophilus influenzae* type b (Hib) was a common cause of childhood osteomyelitis, but its prevalence has been abated by introduction of the Hib conjugate vaccine [2,4]. Organisms such as *Mycobacterium*, *Bartonella*, fungi (*Histoplasma*, *Cryptococcus* and *Blastomyces*), *Candida* and *Coxiella* are unusual causes of osteomyelitis, generally seen in patients with specific risk factors, most notably travel to or residence in geographic regions in which the offending pathogens are endemic and/or immunosuppression [4]. It is also important to note that despite the increasing use of more sensitive diagnostic techniques that are less reliant on culture of the offending bacterium, most notably PCR, the etiology of AHO in children remains unknown in a significant number of cases [5].

As an example, a recent report found that *K. kingae* was the most common cause of osteoarticular infections in French children younger than 3 years of age [6]. However, approximately 70% of these cases were limited to septic arthritis, with only approximately 18% exhibiting clinical evidence of osteomyelitis [6]. This is consistent with a review of

pediatric cases in North America, which found that, other than Gram-positive cocci, *K. kingae* was a primary cause of osteoarticular infections in children younger than 5 years of age [4]. This is also consistent with our experience at Arkansas Children's Hospital (AR, USA) where we have found that *K. kingae* is the most common cause of septic arthritis in children less than 2 years of age [Juretschko S, Arkansas Children's Hospital, Pers. Comm.]. *K. kingae* is a fastidious organism that is difficult to culture, and its apparently increasing prevalence as a causative agent of osteoarticular infections is unlikely to be due to a change in the overall epidemiology of the disease but rather to the increasing use of more sensitive diagnostic techniques, such as PCR, for the direct identification of pathogens present in joint fluid and bone specimens. Such studies emphasize the need for alternative diagnostic techniques that can be used to guide definitive antimicrobial therapy. However, they do not alter the conclusion that Gram-positive cocci generally, and *Staphylococcus aureus* in particular, are by far the single most predominant cause of all types of osteoarticular infections in children of all age groups [2,4].

As with all forms of *S. aureus* infection, the continued emergence of methicillin-resistant strains is an increasing concern. A survey of data from 33 different children's hospitals representing 17 of the 20 major metropolitan areas in the USA found that the prevalence of osteomyelitis caused by methicillin-resistant *S. aureus* (MRSA) increased from 0.3 to 1.4 per 1000 hospital admissions between 2002 and 2007, while the rate of methicillin-sensitive *S. aureus* (MSSA) osteomyelitis remained stable [7]. Overall, 51% of the patients admitted with *S. aureus* infection were infected with MRSA [7]. This is consistent with our experience at Arkansas Children's Hospital, where we have found that approximately 65% of our inpatient *S. aureus* infections are caused by MRSA [Juretschko S, Arkansas Children's Hospital, Pers. Comm.]. Importantly, in a study of all children admitted to Children's Medical Center of Dallas (TX, USA) with acute osteomyelitis between 1999 and 2003, the complication rate of infection secondary to MRSA was considerably greater than that for patients infected with MSSA and for patients suffering from acute osteomyelitis caused by organisms other than *S. aureus* [8]. Complications included myositis, bone abscess, pathologic fracture, deep venous thrombosis and disseminated disease [8]. Of note in that study, children who received appropriate MRSA therapy within 2 days had a similar rate of complications to children who had a 2-day or longer delay in initiating appropriate antibiotic therapy for MRSA acute osteomyelitis [8]. This implies that the use of appropriate antimicrobials alone may not be sufficient to treat MRSA-associated osteomyelitis. This is particularly true with infections caused by CA-MRSA in that these patients often exhibit a more serious clinical presentation, which includes an enhanced inflammatory response, multifocal disease and more frequent bone abscesses requiring surgical drainage [8,9,10]. In this respect, it is important to note that the time frame of the Dallas study [8] corresponds to the time at which the emergence of CA-MRSA infections had begun but had not yet (or perhaps even now) reached its zenith.

Clinical manifestations & diagnosis of acute hematogenous osteomyelitis

Most children and adolescents with AHO present with a history of bone pain for several days [2,4]. The hallmark of AHO pain is its constant nature, with the level of pain increasing gradually [2,4]. In young children, it is often difficult to elicit pain location, while in older children it is typically more localized [2,4]. Pain generally leads to restricted use of the involved limb [2,4]. As the sites most often involved are the long bones of the lower limbs, children frequently present with a limp [2,11]. In all cases, localized bone pain and fever should raise the clinical suspicion of AHO. Exaggerated immobility of the joint and lack of point tenderness over the metaphysis suggest septic arthritis rather than (or in addition to) osteomyelitis. The classic signs of inflammation (redness, warmth and swelling) do not appear unless the infection has progressed through the metaphyseal cortex into the subperiosteal space [2]. Such progression is more common in infants and young children who have a thinner bone cortex.

Elevated erythrocyte sedimentation rate (ESR), elevated C-reactive protein (CRP) and leukocytosis are often seen in AHO, with an elevated CRP being the most sensitive laboratory parameter [12]. However, this is also dependent on the offending agent. For example, a recent study found that a markedly elevated CRP level (>4 mg/dl) was seen in 86% of children with AHO caused by MRSA but in only 58% of children with acute MSSA osteomyelitis [8].

Since physical examination and laboratory tests are suggestive rather than definitive, various imaging techniques have been used to facilitate the diagnosis of osteomyelitis. These include plain radiographs, skeletal scintigraphy, computed tomography (CT) and magnetic resonance imaging (MRI).

Plain radiographs are essential for excluding other diagnoses such as fracture. Although deep soft tissue swelling can be seen radio-graphically within the first few days of onset, osteopenia or osteolytic lesions from destruction of bone are usually not visible until 2–3 weeks after symptom onset [13]. For this reason, the diagnostic utility of plain radiographs for diagnosing osteomyelitis is limited to those patients with prolonged symptoms and, as noted previously, this is generally not the case in children. As a result, other imaging techniques are more commonly used to diagnose pediatric AHO [13]. Skeletal scintigraphy using technetium-99m diphosphonate allows for a whole-body survey, which is useful for those patients with poorly localized symptoms or if multifocal osteomyelitis is a concern, and this has a reported sensitivity of more than 90% [14]. However, it necessitates exposure to ionizing radiation, and sensitivity is lower in neonates, making skeletal scintigraphy less useful in this age group. Differentiation of osteomyelitis from infarction associated with sickle cell disease and other disorders unrelated to infection, including neoplasms and fracture, can also be difficult [14]. In addition, skeletal scintigraphy may have limited utility in diagnosing community-acquired *S. aureus* osteomyelitis. A recent study found that skeletal scintigraphy diagnosed osteomyelitis in only 53% of children with community-acquired *S. aureus* osteomyelitis [15].

One benefit of CT scanning is that it provides specific anatomic information about the status of infection [13]. CT can detect sequestra (indicative of chronic osteomyelitis) and intra-osseous gas, and can define subperiosteal abscesses, all of which are important considerations when designing the overall therapeutic approach [13]. However, CT also requires exposure to radiation. There are studies suggesting that fluorodeoxyglucose positron emission tomography (FDG-PET) may be a useful alternative for diagnosis in adults, particularly when combined with CT [16,17]. However, this issue has not been adequately examined in the specific context of the pediatric patient. MRI can be used to identify intra-osseous, subperiosteal and soft-tissue abscesses, thus enabling early abscess drainage without exposure to radiation [13,18]. Edema and exudates within the medullary space are common findings of acute osteomyelitis and can be visualized by MRI [13,18]. However, these findings can also be seen in other conditions such as fracture and infarct [13,18]. Myositis is also readily identified by MRI [18]. MRI yields better anatomic information, providing an anatomic atlas for orthopedists should surgery be indicated. For these reasons, MRI is becoming the imaging modality of choice for AHO in children [2,13–15,18]. The sensitivity and specificity of MRI for the diagnosis of osteomyelitis range between 82–100% and 75–96%, respectively [13]. Cost, availability and the need for sedation are important limitations to the use of MRI.

While patient presentation, laboratory testing and diagnostic imaging are all important, none are definitive with respect to a diagnosis of AHO and, more importantly, none provide information about the antibiotic-resistance status of the offending organism. For this reason, isolation of the causative organism remains the diagnostic gold standard and is currently the only way to establish a definitive microbiologic diagnosis [1,2]. In a significant number of cases, it is not possible to establish a definitive bacterial etiology, either because the offending organisms are difficult to cultivate or because empiric antimicrobial therapy has compromised

microbiologic analysis [2,5]. When the etiologic agent can be identified, empiric antimicrobial therapy should be adjusted based on the specific susceptibility profile of the offending bacterial strain. Cultured samples should include bone samples, which have a higher diagnostic yield in comparison with blood cultures [2]. However, blood cultures should also be obtained, as an organism is recovered in approximately 50% of all AHO infections [2]. Needle aspiration of the affected bone can be performed using relatively noninvasive procedures in neonates and young children, while older children and adolescents often require more invasive surgical techniques such as drilling or cutting into the bone. Direct inoculation of cultured material into a blood culture bottle increases the probability of recovering a fastidious organism such as *K. kingae*. Using PCR to identify pathogens from bone specimens is also increasingly common. At Arkansas Children's Hospital, all bone specimens are sent for PCR analysis focusing on *S. aureus*, *S. pneumoniae* and, in children less than 8 years of age, *K. kingae*. Fungal and mycobacterial stains and cultures should also be obtained, particularly in cases with specific risk factors and in culture-negative cases of AHO that are unresponsive to empiric therapy. Tissue samples should also be sent for histological examination to confirm the diagnosis of osteomyelitis. Acquiring cultures early in the course of AHO is helpful because prolonged empiric antimicrobial therapy decreases the chance of recovering the causative agent. Indeed in a stable patient, if a plan is in place to rapidly obtain tissue cultures, it is our opinion that empiric antibiotic therapy should be delayed until tissue cultures are obtained.

Treatment of acute hematogenous osteomyelitis

The treatment of AHO demands appropriate antimicrobial therapy in all cases and may require surgical incision and drainage. For the reasons discussed earlier, appropriate drainage has become particularly important in recent years owing to the continued emergence of CA-MRSA. Incision and drainage should be performed whenever an abscess (intra-osseous, subperiosteal and/or soft-tissue) exists [2]. Surgical removal of devitalized bone and debridement of affected soft tissues should be undertaken [1,2]. It has been our experience that multiple incision and drainage procedures are often necessary in children and adolescents with CA-MRSA osteomyelitis, even with appropriate antibiotic therapy. Surgical drainage should also be considered when a child does not respond to empiric antibiotic therapy. In that case, surgical intervention may enhance treatment. In addition, surgical intervention allows for the collection of tissue which can be microbiologically evaluated for unusual etiologies of osteomyelitis, and histologically examined to confirm the diagnosis.

Whether or not surgical intervention is required, the successful treatment of all forms of osteomyelitis requires appropriate antibiotic therapy [1,2,4]. Antibiotics that have proven efficacy against *S. aureus* bone and joint infections include nafcillin, clindamycin, first-generation cephalosporins and vancomycin [1,2]. If MRSA is not a concern (communities with $\leq 10\%$ CA-MRSA determined by local antibiogram) then in our opinion empiric therapy for children (children defined here as those 3 months of age and older) should be an anti-staphylococcal penicillin (nafcillin and oxacillin) or first-generation cephalosporin (cefazolin). These agents are effective not only against MSSA but also against other causes of AHO including *S. pyogenes* and *K. kingae*. Unfortunately, the persistent emergence of MRSA among community-associated isolates has limited treatment options in that all β -lactam antibiotics are eliminated from consideration.

In communities with 10% or more CA-MRSA, vancomycin or clindamycin (if local clindamycin resistance rates are $\leq 25\%$) should, in our opinion, be used for empiric treatment of children. However, it should be noted that neither vancomycin nor clindamycin are active against *K. kingae*. If clindamycin is considered for treatment, the inducible macrolide, lincosamide and streptogramin B (MLS_B) resistance phenotype must be excluded by the D-test (an erythromycin-induction test that shows blunting of the clindamycin zone of inhibition

on the side of a nearby erythromycin disk when the MLS_B resistance phenotype is present), as this phenotype has been associated with treatment failure [19,20]. In our opinion, vancomycin is the primary choice for therapy in the setting of clindamycin-inducible resistance and in communities with clindamycin resistance rates of more than 25%. If *K. kingae* is of particular concern in an area with significant MRSA, consideration should be given to therapy with cefazolin in addition to appropriate MRSA empiric therapy. It should also be emphasized once again that if cultures yield a definitive diagnosis, antimicrobial treatment should be adjusted immediately based on the susceptibility profile of the offending organism. Figure 1 is an algorithm for the suggested initial antibiotic therapy of AHO in children 3 months of age and older.

Trimethoprim-sulfamethoxazole (TMP-SMX) has been used successfully for the treatment of skin and soft-tissue infections (SSTIs) caused by CA-MRSA. However, the effectiveness of TMP-SMX in the treatment of MRSA osteomyelitis in children has not been adequately studied. Similarly, doxycycline can be an effective option for the treatment of susceptible MRSA SSTIs in children older than 8 years of age, but its use for the treatment of MRSA osteomyelitis in children remains unstudied. New antimicrobial agents have also become available for the treatment of infections caused by MRSA in recent years. These include linezolid (an oxazolidinone antibiotic) and daptomycin (a lipopeptide antibiotic). So far, clinical experience with these drugs in the specific context of bone infection in children is limited, although in one study of 13 children treated with linezolid as step-down or alternative therapy for osteoarticular infections, 11 of the 13 children did well [21]. The mean duration of therapy was 20 days and during the course of therapy, two children developed anemia [21]. Myelosuppression is a known side effect of prolonged therapy with linezolid, as are optical and peripheral neuropathies. For this reason, a treatment course of longer than 21 days is not recommended. This limits the use of linezolid in the treatment of AHO in children, which requires prolonged antimicrobial therapy. Pediatric studies of daptomycin efficacy are lacking. Daptomycin use for AHO in children is limited as MRSA AHO complicated by pneumonia is an increasing problem, and daptomycin is inactivated by lung surfactants and cannot be used to treat such complicated infections. Daptomycin is also known to cause creatinine phosphokinase elevation. Creatinine phosphokinase levels should be monitored closely if daptomycin is used, as dangerous rhabdomyolysis can occur. Recent studies have found that daptomycin is particularly effective in the specific context of a biofilm [22] and in the treatment of biofilm-associated infections, including those caused by MRSA [23–25]. This could be particularly important, specifically in the context of chronic osteomyelitis.

Standard therapy for AHO ranges from 4 to 6 weeks in duration. Evidence-based data about the route and duration of antibiotic administration for AHO are limited and criteria establishing when to change from parenteral to oral therapy are undefined [26]. Prolonging antibiotic treatment may be necessary if there is delayed or incomplete surgical evacuation or if there are distant foci of infection (i.e., endocarditis). Interventional radiological placement of indwelling venous catheters in a peripheral vein is readily available, but the costs of catheter placement, home intravenous antibiotics and home nursing care are considerably higher than those required for oral therapy. In addition, complications associated with central venous catheter placement such as bacteremia arising from the indwelling device and line malfunction are relevant considerations. In a review comparing the outcome of a short (<7 days) versus a long (>7 days) course of intravenous treatment for AHO caused primarily by MSSA in children 3 months to 16 years of age, 12 prospective studies revealed an overall cure rate of 95.2% (95% CI: 90.4–97.7) for the short course compared with 98.8% (95% CI: 93.6–99.8) for the longer course at 6 months [26], which is a modest difference in light of the potential complications and costs noted above. In addition, there was no significant difference in therapeutic outcome based on the duration of oral therapy between the two groups [26].

It has been our experience that children can be effectively treated with sequential parenteral/oral therapy provided several conditions are accepted. Parenteral antibiotics should be given until the child is afebrile and has demonstrated improvement by both physical assessment and laboratory analysis. We recommend 7–14 days of parenteral therapy for bacteremic patients; a shorter course of intravenous therapy is acceptable for nonbacteremic children. At the outset of treatment, CRP and ESR should be monitored weekly to assess the response to therapy. The CRP typically returns to baseline within a week of effective therapy and is used by many as a marker for the transition from parenteral to oral therapy [2]. A complete blood count should be obtained weekly to evaluate the response to therapy and to monitor for neutropenia, a potential consequence of antibiotic therapy. The total duration of therapy should be based on the resolution of symptoms and normalization of ESR, which typically takes 4–6 weeks. Reliable caregivers must be present and regularly scheduled outpatient follow-up should be arranged. The oral antibiotic must demonstrate excellent bone penetration, have the same degree of antibacterial coverage as the parenteral drug, and the child should have the ability to take oral medications. However, with the increasing occurrence of CA-MRSA that is also resistant to clindamycin, and a lack of studies concerning the use of other oral antibiotics in children, meeting these criteria may soon prove to be difficult in the USA.

Expert commentary & five-year view

Prior to the introduction of antibiotics, AHO was a serious disease with high morbidity and mortality [2]. With improved diagnostic and treatment methods, mortality from this disease in the developed world is now negligible [4]. However, the variable clinical course of children with AHO makes standardized therapy recommendations difficult. Treatment should always be individualized with a team approach that includes input from pediatric infectious diseases specialists and orthopedists.

The epidemiology of AHO in children has also changed with the emergence of CA-MRSA as a primary pathogen. Past studies of the clinical course, diagnosis and treatment of AHO may not be applicable to CA-MRSA, and for this reason further investigations into all of the issues discussed in this review are urgently needed. It is imperative that these studies include the evaluation of new antimicrobial agents that are effective against staphylococcal strains which are resistant to current β -lactam, lincosamide and glycopeptide antibiotics. These include the lipoglycopeptides (bactericidal agents with long half-lives) telavancin, oritavancin and dalbavancin, all of which are derived from existing glycopeptide antibiotics and some of which are effective against vancomycin-resistant strains [27]. Other antibiotics include iclaprim, a dihydrofolate reductase inhibitor with the potential for oral formulation, and the new cephalosporins ceftobiprole and ceftaroline [27]. It is important that the efficacy of all of these new antibiotics is evaluated in the specific context of children and the more specific context of childhood osteomyelitis.

Irrespective of the availability of any new antimicrobial agents, a major therapeutic concern in all forms of osteomyelitis is being able to initiate the most appropriate therapy as rapidly as possible. Two considerations are important in this respect, the first being the difficulty associated with confirming the existence of infection in a timely manner and the second being the ability to identify the offending pathogen and assess its antibiotic-resistance profile. Because the conventional methods of physical and laboratory analysis have limited specificity, addressing the first of these will require the development of specific imaging modalities capable of differentiating infection from other forms of inflammation and, equally importantly, determining the stage of infection as a necessary prerequisite to developing an effective treatment approach. One possibility in this regard is FDG-PET, although once again the diagnostic utility of this imaging modality has not been adequately evaluated, particularly in the specific context of childhood osteomyelitis. Identification of the etiologic agents of AHO

from bone and blood specimens in a timely fashion is likely to be enhanced by the increased use of molecular diagnostic methods, including PCR.

Finally, while AHO is currently the most common form of osteomyelitis in children, this may begin to change in light of the emergence of CA-MRSA infections. CA-MRSA strains, particularly those of the USA300 clonal lineage [3], exhibit enhanced virulence that translates into complications both in the context of osteomyelitis itself and the occurrence of disseminated infections in pediatric patients. For this reason, it seems likely that the effective treatment of pediatric osteomyelitis will increasingly require therapeutic approaches more commonly associated with chronic infection, including surgical debridement and localized antibiotic delivery. Localized antibiotic delivery offers several advantages, the most important of which is the ability to attain high levels of antibiotics at the site of infection without risking systemic toxicity. Based on this, we believe that a research focus should be placed on the development and evaluation of both stable and bioabsorbable matrices for localized antibiotic delivery. The most commonly used delivery matrix, particularly in cases in which debridement results in a structurally-unstable defect that requires subsequent reconstruction, is polymethylmethacrylate (PMMA). Antibiotic-impregnated PMMA beads are commercially available in some countries, while in others, surgeons must manufacture their own PMMA beads. The alternative approach is implantation of a bioabsorbable delivery matrix, which is appropriate in patients in which surgical debridement does not create a structurally unstable defect. Indeed, in such cases, the use of a bioabsorbable delivery matrix is preferable to PMMA because it does not require removal of the beads at the completion of therapy [28,29].

Irrespective of the delivery matrix, the most commonly used antibiotics are gentamicin, tobramycin and vancomycin, with relatively little experimental data available with respect to other antimicrobial agents. It has recently been demonstrated that daptomycin can be incorporated into both PMMA and other delivery matrices (e.g., calcium sulfate) without a loss of activity and that it retains this activity as it is eluted from the beads over time [30–32]. Clinical experience with antibiotic-impregnated beads in the context of bone infection, particularly with respect to these newer antibiotics, is limited in adults but even more so in children. As noted above, it is essential that all forms of therapy using any of the available antibiotics are evaluated based on both efficacy and pharmacologic considerations in the specific context of pediatric infection. Based on this, it is imperative that future studies examine the use of both existing and new antibiotics in the specific context of localized antibiotic delivery in the treatment of childhood osteomyelitis.

Key issues

- In children, osteomyelitis is primarily hematogenous in origin and acute in nature.
- *Staphylococcus aureus* is the predominant pathogen causing osteomyelitis.
- Methicillin-resistant *S. aureus* (MRSA) prevalence has increased globally, thus altering the epidemiology of osteomyelitis.
- Infections caused by community-associated MRSA (CA-MRSA) have a more serious presentation than methicillin-susceptible *S. aureus* acute hematogenous osteomyelitis.
- MRI is the imaging modality of choice for acute hematogenous osteomyelitis in children, but given the current limitations of all imaging techniques, the development and optimization of alternative imaging modalities is an important clinical objective.

- If the etiologic agent of osteomyelitis is identified, specific antimicrobial treatment based on the susceptibility profile of the organism should be given. To facilitate this, appropriate cultures, including bone biopsy, and alternative diagnostic modalities capable of detecting pathogens irrespective of their growth characteristics (e.g., PCR) should be obtained whenever possible.
- In communities with greater than 10% CA-MRSA, vancomycin or clindamycin should be used for empiric treatment of acute hematogenous osteomyelitis. Vancomycin is the primary choice for therapy of CA-MRSA in communities with clindamycin resistance rates of more than 25% and in the setting of clindamycin-inducible resistance.
- Standard antimicrobial therapy for acute hematogenous osteomyelitis ranges in duration from 4 to 6 weeks. Evidence-based studies regarding the route and duration of antibiotic treatment for acute hematogenous osteomyelitis are limited and guidelines on when to change from parenteral to oral therapy are unavailable.
- The variable clinical course of children with acute hematogenous osteomyelitis makes standardized therapy recommendations difficult. Treatment should always be individualized with a team approach that includes input from specialists in both pediatric infectious diseases and orthopedics.

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Figure 1. Algorithm for the suggested initial antibiotic therapy of acute hematogenous osteomyelitis in children 3 months of age or older

If cultures yield an organism, antimicrobial treatment should be adjusted immediately (as needed).

*If *Kingella kingae* is of particular concern, add therapy with cefazolin.

‡If clindamycin is considered for treatment, the inducible macrolide, lincosamide and streptogramin B resistance phenotype must be excluded by the D-test, as this phenotype is associated with treatment failure.

AHO: Acute hematogenous osteomyelitis; CA-MRSA: Community-acquired methicillin-resistant *Staphylococcus aureus*.