



OSTEOMYELITIS AND SEPTIC ARTHRITIS IN CHILDREN: REVIEW

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ABSTRACT

Purpose of review: The cause, epidemiology, diagnosis, and treatment of osteoarticular infections have changed considerably in recent years. The current review includes the most up to date literature on pediatric septic arthritis and osteomyelitis.

Recent findings: There is controversy over whether osteoarticular infection rates are increasing or decreasing. Changes in epidemiology may be related to improved methods of diagnosis. The pathogens responsible for osteoarticular infections in children have changed with alterations in immunization practices, emergence of resistant bacteria, and changes in patterns of immune modulating diseases and medications in children. Special culture techniques and PCR may help to identify pathogens that are difficult to culture. Surgical debridement is typically required for joint infections and chronic osteomyelitis, whereas acute osteomyelitis can typically be treated with medication alone. Needle aspiration/irrigation alone has been described as an alternative to surgical incision/drainage for septic arthritis, but this practice has not been widely adopted. Intravenous antibiotic therapy for 2–4 days followed by 20 days of oral therapy is effective for treating uncomplicated cases of osteomyelitis, whereas 2–4 days of intravenous antibiotics followed by 10 days of oral therapy is sufficient for septic arthritis. Steroids have shown some improved short-term clinical outcomes in patients with septic arthritis.

Summary: Up to date knowledge of emerging pathogens, utilization of modern diagnostic techniques and implementation of new shorter treatment regimens can optimize the treatment of pediatric septic arthritis and osteomyelitis.

Keywords: Antibiotics, MRI, osteomyelitis, septic arthritis, steroids.

INTRODUCTION

Osteo articular infections can be limb or life threatening. Timely diagnosis and appropriate treatment are paramount to minimizing complications and optimizing outcomes. The current review focuses on recent developments in the cause, epidemiology, diagnosis, and treatment of pediatric septic arthritis and osteomyelitis. In many cases infection may coexist in more than one anatomic location and more than one tissue type[1]. Illness severity has been linked to the primary infection location, and presence of infection in adjacent tissues. Other factors, including patient age and comorbidities, and the species and strain of the responsible microbe, also affect illness severity and response to treatment. In developed countries, recent reports of osteomyelitis rates are 2 to 13 per 100000 children[1, 2]. Higher rates have been reported in developing countries[3, 4]. Osteomyelitis is approximately twice as common as septic arthritis. There is a near equal distribution amongst male and female children. The mean age at diagnosis is 6.6 years[4]. Some studies have reported a decreasing rate of musculoskeletal infections over time, whereas others have reported a significant increase[4]. A recent study reported a 2.8-fold increase in osteomyelitis over the past 20 years, whereas septic arthritis rates have remained constant over this period[1]. MRI is being used more frequently than in the past[5], and it may be that rates of osteomyelitis may not have changed considerably, but detection methods are better than in the past.

Pathogens:

The pathogen most commonly responsible for septic arthritis and osteomyelitis depends on the child's age, comorbidities, socioeconomic, and immune and vaccination status. There are also significant geographic variations in prevalence of different bacterial species and resistances. *Staphylococcus aureus* is typically described as the most common cause of musculoskeletal infections in children[6]. However, gram-negative bacteria may account for 60% of musculoskeletal infections in children under the age of 4, and, in a recent Swiss study, *Kingella kingae* caused 82% of all osteoarticular infections in children under 4[7]. *Hemophilus influenzae B* (HiB) was previously a common cause of osteoarticular infection in young children. In the 1990s widespread vaccination programs were initiated, and HiB infections dropped significantly. A retrospective Canadian study found that 5% of osteomyelitis and 41% of septic arthritis was caused by HiB prior to the vaccination program, whereas no cases were reported in the following years[8]. HiB should still be considered in the differential in unvaccinated children and in developing countries. *Kingella kingae* is emerging as a common cause of osteoarticular infections. In the Swiss study in which *Kingella kingae* was isolated in 82% of osteoarticular infections in children under 4, the authors reported a more benign presentation and course, with only 15% febrile during admission, and 39% having a normal C-reactive protein (CRP)[7]. A recent retrospective review found that age of diagnosis in children with *Kingella kingae* was significantly younger than in children with *Staphylococcus aureus* septic arthritis, and that the clinical course was more benign, but that otherwise all presenting features and clinical markers were equivalent[9]. A predictive algorithm has been

produced for *Kingella*, and this includes temperature below 38°C, CRP below 55 mg/l, white blood cells (WBC) below 14000/mm³, and bands below 150/mm³[10]. *Kingella kingae* is notoriously difficult to culture. In one series, all cases of *Kingella kingae* osteoarticular infection were gram stain and culture negative, but subsequently identified by real-time PCR assay specific to the *Kingella kingae* RTX toxin[7]. Methicillin-resistant *Staphylococcus aureus* (MRSA) has been increasingly reported in recent years. There is significant geographic variation in MRSA prevalence, with no MRSA found in osteomyelitis in Saudi Arabia or osteoarticular infections in Finland[11], whereas in the US MRSA has been implicated in 30–40% of osteoarticular infections[12]. Panton-Valentine leukocidin (PVL) is a necrotizing toxin that is secreted by some forms of methicillin-susceptible *Staphylococcus aureus* (MSSA) and MRSA. It is associated with more invasive osteoarticular disease including higher rates of septic shock, longer hospital stays, and need for prolonged antibiotic and more surgical interventions[13]. It is more commonly associated with MRSA than MSSA, and is thought to be responsible for the increased virulence seen in many cases of MRSA[14]. Altered immune status can make children susceptible to different pathogens. In a recent study comparing osteoarticular infections in HIV-positive with HIV-negative children[15], *Streptococcus pneumoniae* was the causative organism in 67% of HIV-positive children, whereas it caused only 10% of infections in HIV-negative children. The authors recommended that broader empiric antibiotic coverage be used before culture results are available in children known to be HIV-positive, or in areas with a high prevalence of HIV.

Evaluation:

Children with septic arthritis or osteomyelitis typically present with localized pain and swelling, limited range of motion, and difficulty or refusal to weight bear or use an extremity (pseudo paralysis). In a recent systematic review including 12000 patients with acute and sub-acute osteomyelitis[4], 81% presented with pain, 70% showed localized signs and symptoms, 62% presented with fever, 50% had reduced range of motion, and 50% had reduced weight-bearing. There is no single test that can confirm or rule out septic arthritis or osteomyelitis. A combination careful history, physical exam, imaging, laboratory tests, and aspiration / biopsy is typically required to make a definitive diagnosis.

Imaging:

Radiographs should be the first imaging study performed, although they are frequently negative in septic arthritis and early osteomyelitis. Ultrasound is useful for assessing effusion in suspected septic arthritis. If increased fluid is identified, arthrocentesis can be performed under image guidance. Ultrasound of potential septic joints in the emergency room has been shown to have high sensitivity and specificity[16, 17]. Ultrasound is less helpful in the diagnosis of osteomyelitis, although abscesses and periosteal abnormalities may be visualized. Bone scan can be useful when potential infection is poorly localized or multifocal disease is suspected. However, false-negatives have been reported in up to 50% of cases[18]. Early MRI is helpful in the diagnostic process to better classify the location and extent of disease and to plan surgical interventions[1]. A

recent study has shown that community-acquired MRSA (CA-MRSA) frequently affects the non-ossified cartilage of bones, and that on standard MRI sequences this involvement is frequently missed. However, gadolinium enhancement enables identification of these involved areas, and is recommended in suspected cases[19]. Another recent study has reported that MRI can be used to help differentiate between *Kingella kingae* osteoarticular infections and those caused by other pathogens[20]. In this study, epiphyseal cartilage abscesses were found only in the *Kingella kingae* infection group. Soft tissue and bone reaction were significantly less in infections caused by *Kingella*. PET/computed tomography (CT) has been described as superior to MRI in monitoring response to treatment for osteomyelitis, as it is better at distinguishing between ongoing infection and reparative activity[21]. However, radiation exposure and access to PET/CT may limit its practical use.

Laboratory Studies:

BLOOD Blood tests are used to assess for potential osteoarticular infections. Peripheral blood is sent for cell count, erythrocyte sedimentation rate (ESR), CRP, gram stain, aerobic and anaerobic culture. In children with osteomyelitis, 36% of patients had elevated WBC count, 91% had elevated ESR, and 81% had elevated CRP. In patients with both osteomyelitis and septic arthritis, 100% had elevated ESR and CRP[4]. In a combined series of children with osteomyelitis and/or septic arthritis, ESR was above 20mm/h in 94% and CRP was above 20mg/l in 95% of patients. ESR and CRP normalized in 24 and 10 days, respectively. Optimal sensitivity was found when combining ESR and CRP (98%). Due to more rapid normalization of CRP, this marker provides a better option for monitoring response to treatment[22].

Laboratory Studies: Joint Fluid or Bone Specimen:

Joint aspirate or bone specimen should ideally be obtained prior to starting antibiotics. For joints and bones that are easily accessible, aspiration/arthrocentesis may be done under conscious sedation in the emergency room. Joints such as the ankle and hip that are difficult to aspirate, and areas of osteomyelitis that are difficult to localize by clinical examination alone, may need to be obtained by interventional radiology. Alternatively, an orthopedic surgeon may obtain specimens intra-operatively by open or image guided techniques.

Analysis of Specimens:

Recent studies have reported that a causative pathogen is not identified (negative cultures) in 33%[6] to 55%[23] of osteoarticular infections. When unusual pathogens are suspected the physician must communicate these concerns with the laboratory, as some pathogens are difficult to culture and may require specific media, growth conditions or prolonged culture time. *Kingella kingae* is known to culture poorly on solid media. Placing joint aspirate in a blood culture tube (purple top) has been shown to increase positive culture

yields[24]. Use of an enriched liquid medium instead of plating on solid media may also increase yields. Other studies have suggested that patients suspected of having *Kingella kingae* should undergo nasopharyngeal culture, as patients with *Kingella* musculoskeletal infection typically have nasopharyngeal colonization, and throat culture returns positive cultures six times more than joint aspirate[25]. Alternatively, *Kingella* can be identified by PCR[26], although this technique is not yet available at many facilities. PCR can provide results within 3h[27]. In addition to identifying difficult-to-culture pathogens, it may also be helpful in early differentiation between MSSA and MRSA, thus ensuring appropriate early antibiotic treatment, minimizing prolonged and expensive broad-spectrum therapy, and potentially decreasing the iatrogenic contribution to development of resistant bacteria.

Decreasing Bacterial Load:

Mechanical removal of bacteria from a septic joint is typically performed by open or arthroscopic means. A recent small series reported a trend towards improved outcomes and significantly shorter hospitalization times in children who underwent arthroscopic debridement for septic hips, compared with open debridement[28]. Unfortunately, arthroscopy is an advanced skill, and may not be available to all patients on an emergent basis. Needle aspiration and irrigation under general anesthesia for the hip has been described[29], although a proportion of patients treated in this manner have been shown to eventually need formal irrigation and debridement. Another recent study has reported an even less invasive strategy, in which pediatric septic arthritis of the hip was treated with a single aspiration and appropriate antibiotics[30]. Good clinical results were reported, with formal irrigation and debridement performed only when there was sub-optimal clinical and laboratory response to antibiotic treatment. In this series invasive surgery was avoided in 81% of patients. Despite these reports, definitive treatment with needle aspiration and irrigation has not been widely adopted. For patients with acute and sub-acute osteomyelitis, irrigation and debridement are not typically required unless there is insufficient clinical response to antibiotic therapy. Chronic osteomyelitis typically does require irrigation and debridement. Clinical response (temperature, pain, use of the extremity) and CRP levels guide the need for ongoing treatment, and need for further surgical interventions.

Antibiotic Selection:

Patients with osteoarticular infections are typically admitted to hospital and started on empiric antibiotics as soon as a joint or bone specimen has been obtained and sent for analysis. Empiric therapy is selected to cover the most likely pathogens, which are determined primarily by local prevalence of infectious agents and resistance levels, the age of the child, and early lab results such as gram stain if available. Selecting a cephalosporin (e.g. Ancef) that covers MSSA and *Kingella* is typical. A study out of Finland showed success with clindamycin as initial empiric therapy[11]. However, in many locations there is MSSA resistance to clindamycin, and/or high prevalence of *Kingella*, which is also typically resistant, and in these scenarios clindamycin would not be the optimal empiric therapy. The decision to cover empirically for MRSA (e.g.

vancomycin) is controversial due to concerns over developing resistances, costs and potential complications with therapy. If vancomycin is selected, a cephalosporin or penicillin to which *Kingella* is sensitive should be added (*Kingella* is typically resistant to vancomycin). Coverage for gram-negatives must be added for neonates and young children.

Length and Route of Treatment:

The length and route of treatment depend on the location of the infection, as well as the clinical and laboratory response to treatment.

Osteomyelitis:

Although osteomyelitis has traditionally been treated with 4–6 weeks of antibiotics, studies supporting shorter treatment times are emerging. A prospective study of septic arthritis and osteomyelitis in children found that 59% of patients could be converted to oral antibiotics by 3 days, and 86% by 5 days [31]. Patients who were converted to oral antibiotics by 5 days received an additional 3 weeks of oral therapy. The mean in-hospital treatment time was 5 days. There were no complications at 1-year follow-up. Recently a randomized controlled trial (RCT) provided 2–4 days of i.v. antibiotics followed by 20 versus 30 days of oral therapy for acute osteomyelitis [32]. No differences were found amongst treatment groups, and the authors recommend that 20 days of oral antibiotics is sufficient provided there is clinical improvement and CRP is normalizing.

Septic arthritis:

A retrospective study of conversion times from i.v. to oral antibiotics for treatment of septic arthritis showed no difference in outcomes when patients were treated with 7.5 versus 18.5 days of i.v. antibiotics with a total course of 4 weeks of antibiotics [33]. A recent RCT treated patients with 2–4 days of i.v. empiric therapy followed by conversion to oral therapy, with a mean total antibiotic treatment duration of 10 versus 30 days [34]. No difference in outcome was identified between groups. This antibiotic regimen was reported as successful, with most patients undergoing reduction of bacterial load within the joint by aspiration only. Only 12% required surgical irrigation/debridement of the joint, based on clinical and laboratory response to treatment.

Steroids:

Recently a randomized controlled trial [35] of children with septic arthritis compared treatment with i.v. dexamethasone, standard antibiotic therapy, and surgical debridement with standard antibiotic therapy and surgical debridement alone. Dexamethasone was associated with less fever and local inflammatory signs, lower acute-phase reactants, and shorter treatment time with i.v. therapy, although total antibiotic treatment time did not differ. No long-term differences in outcomes were identified.

Complications:

A recent study out of Thailand[36] found complications in 29% following pediatric osteoarticular infections. Complications included avascular necrosis, limb-length discrepancy, and pathologic fractures. The authors identified symptoms more than 1 week at presentation, neonatal age at presentation, infection of the hip joint, MRSA infection, and more than 3 days' delay to appropriate antibiotics as predictors of complications. Although MSSA has been found to have a similar course to other causative pathogens[37], a number of complications have been reported following septic arthritis and osteomyelitis, particularly related to CA-MRSA[38]. In a series of 27 patients with CAMRSA osteoarticular infections, 12 required ICU admission, four had acute multisystem failure, seven developed deep vein thrombosis (DVT) and septic pulmonary emboli, and all required at least one surgical intervention. Prompt recognition and treatment of MRSA osteoarticular infections are of particular importance. Despite appropriate intervention, potential for significant morbidity still exists. In a series of children with osteomyelitis, DVT was identified in 10%, with all cases occurring in patients with MSSA or MRSA[39]. Another retrospective review of DVT complications associated with osteoarticular infections has identified that this complication occurs most frequently in boys, more frequently occurs with *Staphylococcus aureus*, and is often associated with pulmonary complications[40]. Fractures following osteomyelitis have been reported more frequently in patients with MRSA[41]. Patients who went on to fracture were found to have more sub-periosteal abscess and larger area of infection at the time of initial MRI compared with patients who did not fracture. The USA300-0114 pulso type was associated with an increased risk of fracture.

CONCLUSION

The cause and epidemiology of septic arthritis and osteomyelitis have changed over recent years and likely will continue to evolve with changes in immunization practices and bacterial resistance patterns. More widespread use of MRI and implementation of bacterial RNA/DNA detection by PCR have improved our diagnostic ability. Recent prospective and randomized trials have shown that shorter antibiotic regimens can successfully treat uncomplicated pediatric musculoskeletal infections, and that addition of steroids has improved short-term outcomes for patients with septic arthritis. Future research could focus on further prospective assessments of shorter antibiotic treatment regimens, and diagnostic protocols, such as PCR, that may allow earlier determination of causative organisms and the appropriate antibiotic therapy.

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