Paediatric bone and joint infection

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Despite advances in understanding and management, paediatric osteoarticular infections continue to pose diagnostic difficulties for clinicians. Delays in diagnosis can lead to potentially devastating morbidity.

No single investigation, including joint aspiration, is sufficiently reliable to diagnose conclusively paediatric bone and joint infection. Diagnosis should be based on a combination of clinical signs, imaging and laboratory investigations. Algorithms should supplement, and not replace, clinical decision making in all cases.

The roles of aspiration, arthrotomy and arthroscopy in the treatment of septic arthritis are not clearly defined. There is a very limited role for surgery in the management of acute haematogenous osteomyelitis.

The ideal duration and mode of administration of antibiotic therapy for osteoarticular paediatric infection is not yet fully defined but there is increasing evidence that shorter courses (three weeks) and early conversion (day four) to oral administration is safe and effective in appropriate cases. Clear and concise antibiotic guidelines should be available based on local population characteristics, pathogens and their sensitivities.

Kingella kingae is increasingly identified through polymerase chain reaction and is now recognised as the commonest pathogen in children aged under four years. Methicillin-resistant Staphylococcus aureus and Panton-Valentine leukocidin-producing strains of Staph. aureus are being increasingly reported.

A multidisciplinary integrated evidence-based approach is required to optimise outcomes.

Further large-scale, multicentre studies are needed to delineate the optimal management of paediatric osteoarticular infection.

Keywords: paediatric; osteomyelitis; septic arthritis

Introduction

Advances in pharmacology and our understanding of acute paediatric osteoarticular infections have led to significant reductions in associated mortality.1,2 These infections are still, however, associated with significant morbidity. This is partly because of increased survival rates, the emergence of new resistant strains, delays in diagnosis and inconsistencies in delivering optimal care.3

Osteoarticular infections in children comprise a spectrum of disorders depending on the localisation of infection, such as osteomyelitis, septic arthritis, a combination of both or spondylodiscitis (not discussed here). The source of infection may be haematogenous, secondary to contiguous infection or secondary to direct inoculation from trauma and surgery. Most are primarily haematogenous in origin and result from symptomatic or asymptomatic bacteraemia4 in otherwise healthy individuals.

Early diagnosis and prompt treatment are of paramount importance in achieving optimal outcomes and reducing the potentially devastating sequelae of permanent impairment (longitudinal growth arrest with subsequent discrepancy in limb length, angular deformity, chronic infection), septicemia, multi-organ failure and death. Management goals have progressed from survival to limb preservation to maintenance of normal limb development and function.2

In this article, we review the current concepts regarding these pathologies and areas of interest for future developments.

Osteomyelitis is the inflammation of bone caused by pyogenic organisms. Various descriptive classification systems have been developed. A description in terms of timing between onset and diagnosis distinguishes between acute (< 2 weeks), subacute (< 3 months) and chronic (> 3 months).5

The majority of paediatric osteomyelitis cases are secondary to haematogenous spread. The infection seeds in the metaphysis where blood flow is rich but sluggish.6 The femur (27%) and tibia (26%) are the most commonly affected sites.2 In anatomical sites where the bony metaphysis is intracapsular, such as the upper end of the femur, the proximal humerus, the proximal tibia and the distal fibula, there can be subperiosteal spread of infection to the adjacent joint space. The epiphyses of children aged less than 18 months are vascularised by transphyseal
vessels. This can facilitate haematogenous spread of bone infection from the metaphysis to the epiphysis and the adjoining joint space, and clinicians should be alert to that possibility. The use of appropriate imaging modalities such as magnetic resonance imaging (MRI) is vital in such cases to appreciate the full extent of the pathology, recognise adjacent spread and ensure that optimal treatment is delivered.

Septic arthritis is the inflammation of a joint caused by pus-forming organisms, most often by means of haematogenous dissemination of bacteria into the vascular synovium. In some cases, spread may be from adjacent foci of metaphyseal osteomyelitis as a result of the skeletal vascular anatomy discussed earlier. Any joint can be affected but the hip and knee joints are the most common.

The acute inflammatory response following bacterial infection leads to a potent immune response and the release of cartilage-degrading enzymes, which, together with bacterial toxins, lead to rapid joint destruction. To optimise outcomes, treatment of septic arthritis requires prompt recognition, rapid and aggressive antimicrobial therapy, and surgical irrigation of the joint in order to clear the factors responsible (bacteria and inflammatory debris) for the potent activation of the immune response.

Epidemiology

The reported incidence of osteomyelitis in developed countries varies between 1 and 13 per 100 000 population, with higher values of up to 200 per 100 000 reported for developing countries. Some authors report decreases in incidence of over 50% in the last three decades, while others report increasing incidence. The reported increase could partly reflect advances in microbiological diagnosis.

Paediatric articular infections are rare, with incidence rates of 1 per 100 000 reported in the developed world over the past few decades. Much higher rates have been reported in developing regions. Most cases occur in children aged under three years. In this age group, septic arthritis is encountered more often than osteomyelitis.

Osteoarticular infections account for up to 1% of paediatric hospital admissions. Boys are more likely to be affected than girls, with 50% of cases occurring in those aged under five years, peaking in children under the age of one year.

Risk factors

Most cases of acute paediatric bone and joint infections affect previously healthy individuals. There are certain subgroups of children that are more susceptible and should be approached with a high index of suspicion: immuno-compromised children (diabetes, malignancy, HIV, those on steroid therapy, malnourished), premature infants and those with chronic illness requiring frequent venesection.

Sickle-cell is a risk factor owing to its microvasculature effects causing bone infarction. Multifocal osteomyelitis is more common than in the rest of the population. The principal causative organism is either *Staph. aureus* or *Salmonella*. Empirical antibiotic guidelines should account for this. Osteomyelitis is still rare, being 50 times less common than a vaso-occlusive crisis.

Clinical presentation

The classic presentation of an infected child with a leucocytosis has become increasingly less common in developed countries. This could be attributed to improved host resistance and less virulent pathogens involved which can often lead to a subacute presentation. In infants and neonates, immune response is not fully developed, and signs and symptoms may be minimal. Prodomal symptoms and recent minor injury are often part of the acute presentation.

A more insidious and variable presentation is common. Features and severity may vary greatly depending on the site of infection, age of the child and the responsible pathogen. In a recent systematic review in acute and subacute osteomyelitis paediatric patients, the most common presenting features were pain (81%), swelling and erythema (70%), fever (62%), reduced joint movement or pseudoparalysis (50%) and reduced weight-bearing or a limp (49%). Pelvic osteomyelitis is especially difficult to diagnose, causing significant delays in treatment.

Joint sepsis may present with the typical features of an effusion, local erythema, warmth, tenderness, reduced range of movement and systemic features of sepsis. This can be variable, however, with cases often presenting with minimal local symptoms, irritability, reluctance to weight-bear, pseudoparalysis and malaise.

Inflammatory markers

A systematic review on acute osteomyelitis found a leucocytosis in 36% of children on presentation, raised erythrocyte sedimentation rate (ESR) in 91% and raised C-reactive protein (CRP) in 81%. The sensitivity is highest (98%) when both the ESR and CRP are raised.

A similar review in paediatric joint infections highlights the variable inflammatory marker response. White cell count (WCC) response is age-related, with infants and neonates rarely producing a leucocytosis. ESR in isolation has been shown to have a variable sensitivity and is most useful in combination with other parameters, such as those set in Kocher’s criteria. CRP has been shown to have a high predictive value, and a more conservative approach is advocated in the presence of normal values as sepsis is unlikely.

Significant leucocytosis should alert the physician to the possibility of rare or very virulent pathogens.
CRP values > 100 mg/L are particularly significant in osteomyelitis patients for concomitant septic arthritis and are also the best predictor of a complicated course and the need for prolonged intravenous antibiotics. CRP has a short half-life and hence is useful for monitoring response to treatment. Serum procalcitonin has recently been advocated as a potential highly specific marker for bacterial infection that could assist in the diagnosis of osteoarticular infections.

Microbiology specimens

The British Orthopaedic Association (BOA) and British Society for Children’s Orthopaedic Surgery (BSCOS) guidelines recommend that microbiology specimens be taken prior to antibiotic therapy administration but state that this should not delay treatment in unwell children. Samples should be sent for urgent microscopy and gram stain. Synovial fluid WCC > 50 000 with > 80% polymorphs is often seen in joint sepsis but clinical correlation is required as similar results can be seen in inflammatory arthropathies. Gram stain sensitivity has been reported as variable (30% to 80%).

Blood cultures should be sent prior to antibiotic treatment despite their low yield as they are occasionally the only samples to provide a positive yield. Reported overall rates of positive organism identification in blood/tissue samples vary in the literature from 34% to 82%.

Recent studies suggest that tissue and fluid sampling in aerobic media increases their microbiology yield and should be routinely employed. Recently, the addition of polymerase chain reaction and other molecular diagnostics recently has significantly increased positive results. Specimens should also be sent for histopathology as childhood malignancies can present similarly.

Imaging modalities

Plain radiographs should be obtained on admission in order to rule out other pathologies. Skeletal changes of osteomyelitis are generally not visible before day five as periosteal ossification. MRI is the modality with the highest sensitivity (82% to 100%) and specificity (75% to 99%). It offers excellent tissue delineation and allows for detailed evaluation and surgical planning while avoiding radiation hazards. It is not, however, always available and it often requires sedation in the paediatric patient.

Computed tomography (CT) has a limited role in the acute setting due to poor soft-tissue contrast and excessive radiation. It may be employed when MRI is not available or contraindicated. Bone scans can be useful to assist localisation in younger children who cannot verbalise the site of pain. They offer a valid alternative to MRI with sensitivity of 73% to 100% and specificity 73% to 79%. They involve radiation exposure. They have a limited role in neonates due to the decreased sensitivity and they lack sensitivity and specificity in distinguishing septic arthritis from nearby osseous or soft-tissue infections.

Ultrasound is very sensitive (95%) in identifying hip effusions, but despite being useful in the visualisation of subperiosteal collections, has a limited role in differentiating sepsis from other causes of hip effusion. The key role of ultrasonography is to support the suspected clinical diagnosis. It is cheap, safe, non-invasive and portable.

Positron emission tomography with CT has been described as superior to MRI in monitoring response to treatment for osteomyelitis. It is better at distinguishing between ongoing infection and reparative activity and has faster scanning times. Exposure to radiation and limited availability reduce its practical use.

Causative organisms

In up to 55% of cases no organism is identified. Staph. aureus is the most common pathogen in acute osteoarticular infections, being identified in 70% to 90% of culture-positive cases, followed by streptococcal (S. pyogenes and S. pneumoniae) and gram-negative organisms. Salmonella is an important pathogen in sickle-cell patients. Haemophilus influenzae has become rare following worldwide vaccination programmes.

Community-acquired methicillin-resistant Staph. aureus (MRSA) is on the increase in many parts of the world and has been reported as a causative agent in 9% to 30% of children with osteomyelitis. Panton-Valentine Leukocidin MRSA (PVL-MRSA), an extremely virulent strain, has been increasingly reported in the paediatric population. PVL is a toxin that destroys white blood cells and is associated with increased morbidity and mortality. In the context of osteoarticular infections, when presentation is associated with increased systemic and local complications, clinicians should have a high index of suspicion for this emerging strain necessitating more aggressive antibiotic regimes and surgical management. The Health Protection Agency has recently published guidance on the diagnosis and management of these infections.

Kingella kingae (a gram-negative bacillus) is a significant cause of osteomyelitis and septic arthritis in young children, with recent studies suggesting that it is the most common pathogen in children under the age of four years. Despite its identification in the 1960s, this organism has until recently not been fully understood. It is a common coloniser of the oropharynx that can be easily transmitted. Recent advances in laboratory investigations have enabled easier isolation from samples and it has now been recognised as a common pathogen in osteoarticular infections. The mild symptoms and limited increases in acute phase reactants...
Tors.37 Management should involve early input from a microbiologist. Empirical treatment is therefore commonly employed in older children.46

Choice of antibiotic regime
Optimal outcomes are achieved through the prompt administration of antibiotics of appropriate sensitivities and dosages. Culture results are desirable but often not available. Empirical treatment is therefore commonly employed based on local guidelines and patient factors.37 Management should involve early input from a microbiologist.

The BOA/BSCOS guidelines recommend flucloxacillin or a cephalosporin as first-line treatment owing to the dominance of *Staph. aureus* while benzylpenicillin or a cephalosporin should be added in children not immunised against *H. influenzae*. Gentamicin is advocated for gram-negative cover in children aged less than one year. Clindamycin is the drug of choice in penicillin-allergic patients. Broad spectrum combinations should be employed early in high-risk patients for atypical organisms. Local protocols should have provisions for MRSA infections based on local sensitivities. There is wide geographical variation with regard to pathogen prevalence and doctors should be aware of these when considering the underlying pathogens to determine the most appropriate regime. First-line antibiotics may need to be adjusted upon this basis.

Length and route of administration of antibiotics
Traditionally prolonged courses of parenteral antibiotics have been employed. No clear guidelines are established. There is increasing evidence that, in appropriate cases, shorter courses of antibiotics are equally effective37,47,50 with early transition to oral administration.51-53 Response to treatment, such as improvement in clinical symptoms of pain and range of motion, resolution of fever and reduction of inflammatory markers (ESR, CRP, WBC count), can reliably guide clinicians to a safe transition,54,55 reducing intravenous line-related complications and re-hospitalisation rates.

Other treatments
There is no evidence regarding the use of intra-articular antibiotic administration and their use is not recommended. Recent studies suggested a potential beneficial role for intravenous steroid administration in children with septic arthritis.56,57 The introduction of new generation cephalosporins and the use of monoclonal antibodies directed against virulence factors of the causative pathogen could affect outcomes in future.3

Multidisciplinary approach
To improve outcomes, care should be delivered by close collaboration between primary care physicians, emergency department clinicians, paediatricians, orthopaedic surgeons, microbiologists, specialist radiologists and specialist nurses using evidence-based guidelines.58 Regular re-evaluation during treatment, as well as short- and long-term follow-up, should be provided by specialists.

Discussion
Despite significant advances in our understanding of these pathologies, they continue to present diagnostic challenges. There are no ‘gold standard’ tests. Various diagnostic algorithms22,23,25 have been introduced over the years but they should not be used as a substitute for clinical decision making.1

There are still controversies and a lack of a strong evidence base with regard to many aspects of managing these conditions. Recommendations in the literature are generally based on expert opinions, case series and cohort studies. The need for high-quality research (large, multicentre, randomised, controlled trials) has been established.1,2 Guidelines for good practice have recently been introduced in the UK.

The delivery of quality clinical care is optimised in paediatric osteoarticular infections by adopting a multi-disciplinary integrated evidence-based approach.
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