Acute haematogenous osteomyelitis in children

Andrea Yeo, Manoj Ramachandran

Acute osteomyelitis is an uncommon but important disease that affects previously healthy children. A high index of suspicion is required as early treatment is essential for a good outcome. In the past decade, rapid changes in the epidemiology of the condition, in particular of infections as a result of meticillin resistant Staphylococcus aureus (MRSA), and advances in diagnostics have highlighted a need to change practice based on current evidence. We review the pertinent aspects of acute osteomyelitis, highlighting the pitfalls in diagnosis and providing a framework for management.

What is acute osteomyelitis?
Osteomyelitis is the inflammation of bone caused by pyogenic organisms. In the acute setting, the duration of symptoms is less than two weeks. The major sources of infection are haematogenous spread, tracking from adjacent foci of infection, and direct inoculation from trauma or surgery. Haematogenous spread is the most common source of infection in children, typically affecting the long bones. The infection seeds in the metaphysis, where blood flow is rich but sluggish. The femur and tibia are most commonly affected (27% and 26%, respectively, fig 1). In long bones where the metaphysis is intracapsular (the shoulder, ankle, hip, and elbow, in decreasing order of incidence), the infective foci may extend into the joint space, resulting in concurrent septic arthritis. Similarly, in children under 18 months of age, anatomical transphyseal vessels facilitate translocation of bacteria from the metaphysis to infect the epiphysis and adjacent joint, increasing the risk of concurrent septic arthritis.

Who gets osteomyelitis and why is it important?
The incidence of osteomyelitis varies between 1 and 13 per 100 0001 3 and accounts for around 1% of all hospital admissions in children. Boys are nearly twice as commonly affected as girls, with 50% of cases occurring in those under 5 years old,4 peaking in children under 1 year. In most cases the lesion is solitary but can be multifocal (7% of children and 22% of neonates).5

Recent studies have reported an increasing incidence and, more worrying, worsening severity of musculoskeletal infection in children.6–11 A recent large case-control study from the United States reported a 2.8-fold increase in the incidence of osteomyelitis over the past 20 years.11 Over this same period, the incidence of septic arthritis has remained unchanged, occurring half as frequently.11 There has been a concomitant increase in MRSA as the causative organism in most cases of complicated osteomyelitis,6 10 12 with one group reporting a 30% incidence.11

Delays in treatment may lead to complications such as concurrent septic arthritis, subperiosteal abscess, pyomyositis, deep vein thrombosis, permanent impairment (longitudinal growth arrest with subsequent discrepancy in limb length, angular deformity, chronic infection), septic caemia, multiorgan failure, and death. Osteomyelitis and concurrent septic arthritis have been reported at a rate of 3% to 33%.11 13 14 In a cohort of 212 children with osteomyelitis, up to 8% presented with deep musculoskeletal infections of subperiosteal abscess, pyomyositis (2%), or all four (1%)—osteomyelitis, concurrent septic arthritis, pyomyositis, and subperiosteal abscess.15 As can be expected, the more extensive the infection, the greater the clinical manifestation and severity of the illness, with increased requirements for intensive care support, longer hospital stays, and higher complication rates, including deep vein thrombosis (33%).11

The profile of the condition has changed noticeably with vaccinations and the use of antimicrobial treatment; mortality rates of about 50% in the preantibiotics era have fallen to less than 1%, and it is usually from overwhelming septicaemia with involvement of multiple organs.5 10 15 With prompt, effective treatment, prognosis is generally good, with cure rates of more than 95%.5 Management goals have therefore changed from survival to limb preservation to maintenance of normal limb development and function.15

What are the risk factors for osteomyelitis?
Up to half of cases have no risk factors at all, and minor trauma, such as an innocent fall on to the knee, may be the presenting history in up to 30% of cases.6 However, a par-
The femur and tibia are the most commonly affected bones.

**How is osteomyelitis diagnosed?**

The classic florid picture of an unwell, febrile child with a high white cell count is increasingly uncommon. This is speculated to relate to improved standards of living and hygiene; as such, fewer virulent pathogens lead to a more subacute presentation. In subacute osteomyelitis, the balance between the microbe and host is such that the destructive and repair processes do not take place as rapidly as in acute infection.

The onset of osteomyelitis can be insidious, the clinical presentation variable, and the physical findings non-specific. No single test can confirm or rule out acute osteomyelitis. A combination of careful history and examination, accompanied by a high index of clinical suspicion, and followed by laboratory and imaging studies are key parts of the clinical investigations. It should always be borne in mind that childhood malignancies (for example, leukaemia, lymphoma, and neuroblastoma) can present with non-specific musculoskeletal symptoms.

**Clinical features and severity may vary greatly depending on the site of infection, age of the child, and the species of the responsible pathogen.**

In a recent systematic review involving over 12 000 patients with acute and subacute osteomyelitis, the commonest presenting features were pain (81%), swelling and erythema (70%), fever (62%), reduced weight bearing or a limp (49%).

**Box 1 | Differential diagnoses for acute osteomyelitis**

| Vascular                        |  
|---------------------------------|---|
| Vaso-occlusive disease          |  
| for example, bone infarct       |  
| Secondary to sickle cell disease|  
| Infection                       |  
| Septic emboli                   |  
| Chronic recurrent multiple osteomyelitis |  
| Septic arthritis                |  
| Trauma                          |  
| Stress fracture                  |  
| Tumour                          |  
| Osteoid osteoma                 |  
| Acute lymphoblastic leukaemia    |  
| Eosinophilic granuloma          |  
| Metastatic neuroblastoma        |  
| Ewing’s sarcoma                 |  
| Osteosarcoma                    |  

**What investigations can help confirm osteomyelitis?**

A systematic review found that only 36% of children will have a raised white cell count on presentation, 91% an increased erythrocyte sedimentation rate, and 81% an increased C reactive protein value. The sensitivity is highest when both the erythrocyte sedimentation rate and C reactive protein are increased (98%). C reactive protein values >100 mg/L are particularly significant for concomitant septic arthritis and are also the best predictor of a complicated course and the need for prolonged intravenous antibiotics. C reactive protein has a short half life (19 hours) and hence is also useful for monitoring response to treatment.

The British Orthopaedic Association and the British Society for Children’s Orthopaedic Surgery recommend that specimens should be taken, when possible, before starting antibiotic treatment. This recommendation should not, however, lead to a prolonged delay in starting antibiotics, especially in very sick children. Blood cultures may be positive in only 50% of cases, but should still be taken before antibiotics are started as it may be the only positive source of identification of the pathogen.

Bone or joint aspirates can have a higher yield (70%).
Specimens can be obtained through interventional radiology (for example, guided by ultrasound or computed tomography) or surgery; and should be sent for urgent Gram stain and culture. Culture of joint aspirates in commercially available blood culture bottles helps to improve the yield of organisms that are difficult to culture. Additionally, specimens should always be sent for histology as several childhood malignancies may present with similar clinical features.

What imaging studies are useful in suspected osteomyelitis?
Plain radiographs of the affected part often do not show any abnormality in the early phase of infection. However, these are useful to exclude other conditions such as fractures or malignancy. Acute skeletal changes (periosteal elevation, bone destruction, fig 3) are not visible before 5-10 days, but subtle features of soft tissue swelling may be seen (fig 4).

Magnetic resonance imaging is the preferred modality for initial clinical investigations, with high sensitivity (82-100%) and specificity (75-99%). This type of imaging is helpful in identifying the location and extent of disease and offers more detailed evaluation of the adjacent structures in suspected complicated cases, such as pyomyositis, joint effusion, and subperiosteal abscesses. It can also help in assessing difficult sites of infection (for example, pelvic osteomyelitis) and planning surgical intervention.

Magnetic resonance imaging is safe as it carries no risk from radiation; however, young children often require sedation or general anaesthesia before the procedure can be carried out. It also has the disadvantages of higher costs, prolonged imaging time, and difficulties with access, especially out of hours. Whole body magnetic resonance imaging is increasingly used to evaluate multifocal osteomyelitis or in cases where localisation of symptoms is doubtful.

Computed tomography provides excellent multiplanar image reconstructions, allowing delineation of subtle osseous changes; however, its role in the assessment of acute haematogenous osteomyelitis is limited owing to poor soft tissue contrast and high exposure to ionising radiation (compared with magnetic resonance imaging). It is more useful in chronic osteomyelitis, where computed tomography can show sclerotic changes, abnormal thickening of bone, extent of disease, and chronic draining sinuses. Computed tomography can be used for evaluation of complications of osteomyelitis if magnetic resonance imaging is not available or is contraindicated.

Bone scans may also be useful in cases of poorly localised infection—for example, in younger children who cannot verbalise their site of pain, or in multifocal disease. The overall sensitivity and specificity of bone scans are 73-100% and 73-79%, respectively. In neonates, however, the sensitivity decreases (32-87%). It is not clear why the sensitivity decreases in neonates. However, this may relate to false negative scans where “cold” rather than “hot” spots are seen in severe infection. New bone formation and blood flow are important requirements for the uptake of radionuclide on to bone; hence any mechanism that interferes with hyperaemia or osteoblastic activity (for example, thrombosis and tamponade of the affected bone) is likely to produce an image of decreased activity.

Ultrasound cannot evaluate bone marrow (ultrasonic waves cannot penetrate bone cortex) and hence its use in the diagnosis of osteomyelitis is limited. Nevertheless, ultrasonography is a useful investigation for visualising subperiosteal collections and joint effusions, and it can aid in the aspiration of soft tissue fluid and joint. The key role of ultrasonography is to support the suspected clinical diagnosis. It is cheap, safe, non-invasive, and portable. Hence it can be utilised in cases where access to other modalities is not readily available or is contraindicated, such as a child in intensive care where transfer to a magnetic resonance imaging scanner is unsafe.
Which organisms cause acute osteomyelitis?

*Staphylococcus aureus* is the most common pathogen in acute osteomyelitis, being cultured in 70–90% of culture positive cases,1 followed by streptococcal (*S pyogenes* and *S pneumoniae*) and Gram negative organisms. Salmonella is an important pathogen in children with sickle cell disease, especially the non-typical serotypes (*S typhimurium, S enteriditis, S choleraesuis*).3 It has been suggested that tiny infarctions in the gastrointestinal tract lead to salmonella (and other enteric Gram negative) bacteraemia and ultimately to infection.3 Children with sickle cell disease and suspected osteomyelitis may require a completely different antibiotic regimen, and local microbiological advice should be sought. A recent Cochrane review found no randomised trials on antibiotic approaches for osteomyelitis in people with sickle cell disease.36

Over the past few decades the pattern of causative organisms has been changing, with more resistant strains emerging. *Haemophilus influenzae*, previously the most common Gram negative organism in paediatric osteomyelitis, is now rare as a result of the vaccination programmes of the early 1990s.23 Conversely, the incidence of community acquired MRSA is increasing in many parts of the world.1,10,12,29,37 The MRSA epidemic has not only altered antibiotic treatment regimens, but also affected the severity of disease.10,12,29 MRSA is a causative agent in 9–30% of children with osteomyelitis,10,29 and cases have been documented of PVL-MRSA (Panton-Valentine Leukocidin MRSA), an extremely virulent strain.

MRSA osteomyelitis can cause a more aggressive and complicated course, with higher inflammatory markers and fever, prolonged hospital stay, and an increased likelihood for repeated surgical debridement compared with other pathogens.10,11,37 It is also associated with many complications, including multiorgan failure, deep vein thrombosis (10%), septic pulmonary emboli, multifocal infection, subperiosteal abscesses, fractures (20%), and progression to chronic osteomyelitis.11,37,38

*Kingella kingae* is a common pathogen that colonises the respiratory tract and is transmitted from child to child through close contact. *K kingae* osteomyelitis is on the increase, with more than 95% of cases occurring in children under 3 years of age.3 This pathogen tends to present with more benign features, with only 15% of children febrile at presentation and 39% having normal inflammatory markers (C reactive protein and white cell count).3 It is, however, difficult to culture and is mainly identified by molecular techniques of polymerase chain reaction, which may not be readily available.23,39

A causative pathogen is not identified in up to 55% of cases.23 When less common organisms are suspected, such as in a child with an altered immune status who is more susceptible to different pathogens, these must be communicated to the laboratory and discussed with microbiology colleagues, as some pathogens are difficult to culture and may require specific media, growth conditions, or prolonged culture time.23 A systematic review found that culture negative osteomyelitis was successfully treated in the same way as confirmed staphylococcus disease.3

How is osteomyelitis treated?

The care of children with acute osteomyelitis is multidisciplinary, requiring communication and coordination among general practitioners, emergency departments, paediatric infectious diseases, orthopaedics, microbiology, radiology, nursing, and community teams to ensure early diagnosis and effective treatment. In a well designed case-control study, multidisciplinary management has been shown to produce more efficient clinical investigations, higher rates of identifi-
cation of causative organisms, and fewer changes in antibiotics, with lower admission rates and shorter hospital stays.10

The basic goal is to deliver antibiotics in appropriate dosages according to the sensitivities of the causative organism. Antibiotic choice should be guided by culture results and local microbiology advice wherever possible to facilitate a more focused therapeutic regimen. However, to avoid treatment delays, empirical treatment should be selected to cover the most likely pathogens, which is determined primarily by local prevalence of infectious agents and resistance levels, the age of the child, and early microbiological results such as that for Gram’s stain.1, 15

Little evidence, however, exists on the choice of initial antibiotic or the optimal duration of intravenous and oral treatment for acute osteomyelitis in children, as evidenced in a recent systematic review.7 The British Orthopaedic Association and the British Society for Children’s Orthopaedic Surgery recommend flucloxacillin or a cephalosporin as first line treatment owing to the dominance of S. aureus12; although in the United States and Finland, clindamycin is more commonly used.13 Benzylpenicillin or a cephalosporin should be added in children not immunised against H. influenzae.15

Some authors have suggested empirical cover against MRSA, especially if more than 10% of S. aureus isolates are meticillin resistant9 or if the child has recognised risk factors, such as previous admission to hospital or colonisation, or is from an ethnic background in which prevalence is high—for example, Polynesian or Aboriginal. This has not been widely accepted mainly due to fear of inducing selective antimicrobial resistance.3 Broad spectrum cover is especially important in neonates, children with sickle cell disease, and immunocompromised children, who can be infected with a wider variety of organisms.

Acute osteomyelitis has traditionally been treated with 4-6 weeks of antibiotics. However, several small cohort studies have supported shorter treatment regimens, which obviate the complications associated with intravenous lines (for example, infection and allergic sensitisation)22, 41 and allow the child to be managed at home. The transition to oral step-down treatment is guided by improvement in clinical (resolution of fever and pain with restoration of function) and haematological (normalising C reactive protein levels) variables.29

The only randomised trial to deal with the duration of antibiotic treatment showed that oral antibiotics for 20 days was as effective as a 30 day course in patients who had already received intravenous antibiotics for four days, with a good clinical response.30 This has been backed up by a recent systematic review (grade 2B recommendation).1 Evidence on neonates (<3 months) is, however, insufficient to alter the current recommendation of parenteral antibiotics for four weeks owing to concerns about absorption and efficacy of oral antibiotics in this population.1

Routine exploration of acute haematogenous osteomyelitis is no longer recommended by the British Orthopaedic Association and the British Society for Children’s Orthopaedic Surgery.15 A recent systematic review showed that appropriate antibiotic therapy is sufficient and surgery does not confer any additional benefit.1 Surgery is now reserved for circumstances where medical treatment fails or when a major abscess has collected.15 The decision to drain an abscess should be made on clinical grounds (temperature, pain, reduced use of limbs, and increasing C reactive protein values), specifically the response to antibiotics.3 Drainage is required in approximately 20% of pelvic abscesses and 6% of those in long bones.3

What is the prognosis for osteomyelitis?

Acute haematogenous osteomyelitis in children is invariably curable. Recognition of the often subtle features with the help of sophisticated detection tools and early treatment with antibiotics will ensure an excellent outcome with negligible long term sequelae. However, the epidemiology of the disease continues to evolve as immunisation practices and patterns of bacterial resistance change, demanding greater vigilance from clinicians. Box 3 lists the risk factors associated with a worse prognosis.

What does the future hold?

Polymerase chain reaction

Much recent attention has focused on the development of molecular diagnostic technology to identify rare pathogens.4 Polymerase chain reaction is more sensitive and identifies the organism much more quickly than conventional culture techniques do.5

Serum procalcitonin

Detection of serum procalcitonin levels is the most recent diagnostic aid. It reflects the severity of the disease.9 Acute haematogenous osteomyelitis in children is invariably curable. Recognition of the often subtle features with the help of sophisticated detection tools and early treatment with antibiotics will ensure an excellent outcome with negligible long term sequelae. However, the epidemiology of the disease continues to evolve as immunisation practices and patterns of bacterial resistance change, demanding greater vigilance from clinicians. Box 3 lists the risk factors associated with a worse prognosis.

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New treatments

There are concerns about the increased virulence of pathogens and the adequacy of antibiotics to combat them. Two new fifth generation cephalosporins have been recently developed with activity against MRSA (ceftaroline and ceftobiprole). New advances in treatment on the horizon include use of monoclonal antibodies directed against virulence factors of the causative pathogen.

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