Misconceptions about childhood acute osteomyelitis

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Background

Osteomyelitis has been a formidable disease in many countries. Many clinicians continue to implement older treatment regimes due to ingrained fear of chronic disease. The spectre of chronic osteomyelitis with its sequestra and discharging sinuses may over-ride the accumulated but sometimes inaccessible evidence of recent years. The authors believe it timely to correct two misconceptions about acute osteomyelitis that lead to confusion, controversy and cost. It must, however, be stressed that only primary acute osteomyelitis is considered here. When joint involvement, chronic and sub-acute disease, multi-focal disease or an immunologically compromised child are implicated, each must be treated on its own merits.

Pathogenesis

In 1922, the Japanese researcher Teruo Hobo [1] published a paper in German which suggested that acute

osteomyelitis developed in the metaphyses of long bones because of the sluggish blood flow in the capillary loops. Josep Trueta [2], a pioneer of bone blood-flow properties, re-iterated Hobo's theory in his investigations into acute osteomyelitis. In the 1940s, when penicillin first became available, Trueta was in Oxford and had early access to that 'wonder drug'. *Staphylococcus aureus* was responsible for the great majority of acute bone infections, nearly all of which responded to treatment with penicillin alone. This heralded a remarkable change in the outcome of acute osteomyelitis.

Advances in science and technology since Trueta's seminal studies with light microscopy and vessel perfusion techniques have allowed greater precision in studying the junction between the metaphysis and epiphysis of bone. An animal model of acute osteomyelitis subjected to electron microscopy revealed that the Hobo and Trueta theories [3] are no longer fully tenable.

In the acute osteomyelitis of children, bacteria lodge adjacent to the physis, probably in relation to terminal metaphyseal vessels [4]. These vessels are open-ended, as they tunnel between the columns of dividing and decaying physal cartilage cells. It is not the sluggish flow that is critical, but the fact that the vessels are open-ended. As a bone grows in length, it is likely that branches develop from the extending vessels, but not at their ends. Some of those branches may anastomose to form the loops that Hobo and Trueta visualised. However, chondrotropic pathogenic bacteria escape from the open-ended vessels and adhere to cartilage cells at the junction between the physis and metaphysis. Here, they divide and stimulate acute inflammation. This results in vascular engorgement, oedema, polymorphonuclear cellular responses and tissue death secondary to ischaemia from either venous or arterial obstruction. The growing bacterial colonies provoke acute

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suppuration and liquefactive necrosis of medullary tissue. The trabeculae of cancellous bone become fragmented, lose their vascular relationship and die; they remain in the pus as small sequestra.

The basic process in infants is similar but, because of the presence of transphyseal vessels that become obliterated in the first year of life, the infection may spread rapidly across the physis and epiphysis into the joint [5]. Whereas in childhood the infection does not usually involve the germinal cells of the physis and, hence, does not interfere directly with growth, in infants, these cells may be inhibited or die (Fig. 1). A recent review [6], however, continues to suggest that “the majority of osteomyelitis occurs in the metaphysis owing to the blood flow characteristics of its sinusoids.”

The *first* misconception allows the theories of Hobo and Trueta to persist without recognising the pathogenesis advanced by more modern studies.

Antibiotics

Models of acute haematogenous staphylococcal osteomyelitis in animals have allowed its natural history to be clarified. Spread into an adjacent joint occurs early in infants because the transphyseal vessels present in the newborn may persist for several weeks after birth, providing a direct pathway from the metaphysis to the epiphysis. Only when the physis or growth plate loses its transphyseal vessels does it act as a temporary obstacle to bacterial transmission from the metaphysis to the joint.

In February 1941, Trueta held the first infected rat injected with penicillin by Florey. It is worth recalling that the death rate for infantile osteomyelitis was over 30 % in

the pre-antibiotic era. The bactericidal activity of antibiotics supported by our natural immune defence mechanisms has made a fatal outcome much less common.

To be effective, antibiotics need an adequate blood supply to deliver them to the site of infection in bone: dead bone prevents adequate penetration. Antibiotic treatment must maintain a minimum inhibitory concentration (MIC) in the blood, have good tissue penetration and be effective against the causative organism, usually *S. aureus* [7]. Understanding the pharmacokinetics of each antibiotic and its rate of metabolism and excretion allows the proper calculation of dosage and delivery. In general, a similar total daily dose delivered by continuous infusion produces serum concentrations similar to that achieved with appropriate intermittent dosing [8]. If given orally, absorption from the gastro-intestinal tract is affected by numerous factors, especially in a very ill infant. Antibiotic administration by mouth should be administered between meals to optimise serum levels. The dose is determined by the patient's age and body weight.

Studies with flucloxacillin indicate that the MIC is the best predictor of bacterial killing. For methicillin-sensitive *S. aureus* (MSSA) and methicillin-resistant *S. aureus* (MRSA), MICs of 0.1–0.25 mg/L and 0.25–0.5 mg/L, respectively, are recommended. As the MIC is not usually measured in hospital laboratories, it is wise to give two to three times the recommended dose orally compared with intravenous administration to maintain serum levels. A number of studies have shown that the cure rate is not made worse when serum levels are maintained by oral compared with intravenous administration [9, 10]. Initially, antibiotics should still be delivered intravenously but conversion to oral administration should follow when the child is improving clinically and eating normally, usually in

Fig. 1 **a** Photomicrograph of an abscess forming in physal cartilage 1 day after the inoculation of *Staphylococcus aureus* into a vein. This is the earliest example of the formation of an abscess in haematogenous osteomyelitis. **b** Spread of bacteria initially deposited at the growing tip of a metaphyseal vessel, the usual site of adhesion of *S.*

aureus to physal cartilage, can advance into the epiphysis and produce an abscess there because of transphyseal vessels that remain patent during infancy. The abscess is normally found on the metaphyseal side of the physis, as shown in Fig. 1a

3–5 days. As bacteria have become increasingly resistant to penicillin and other antibiotics, it is essential to have a hospital-based policy for their use. Inevitably, the choice of antibiotic for initial therapy is based on a best-guess of the causative organism. As it is usually *S. aureus*, then an anti-staphylococcal bactericidal drug should be chosen in the first instance [11]. A broader spectrum drug is usually prescribed in addition. The precise combination should properly reflect the prevailing sensitivities of organisms in the geographical region and any allergy the child might have. The antibiotic policy should be regularly reviewed and updated.

Complications often follow prolonged intravenous administration of antibiotics for acute osteomyelitis. The incidence of catheter-related infections in Australia is about 1.6 per 100 admissions and the mortality of bloodstream infections is about 12 % [12]. Sepsis associated with the catheter is not uncommon—up to 41 % in one study following more than 2 weeks of intravenous therapy [13]. Mechanical failure, local skin infection, fever with negative blood culture and adverse drug reactions occur. Children may need general anaesthesia to insert a centrally placed catheter. Prolonged hospital stay is often necessary or frequent visits by a community nurse to administer antibiotics at home. Furthermore, considerable expense is incurred by prolonged intravenous therapy. Oral antibiotic therapy does not carry most of these complications!

For how long should antibiotics be given? In the 1970s, six weeks of intravenous therapy was recommended [14]. That contributed to morbidity and cost. The long wait for high-quality clinical evidence to guide management has not been fruitful. One study in 2005 concluded that there was no consensus for the best agent, route or duration! At the European Paediatric Orthopaedic Society meeting in Helsinki, Finland, 2012, treatment by long-term out-patient parenteral antibiotics was again recommended [15].

However, two studies in 1982 and 1987 provided momentum for establishing a shorter course of parenteral administration [16, 17]. These sequential studies of therapy used intravenous antibiotics for 2–5 days, followed by oral therapy for 6 weeks in the first and 3 weeks in the second. The studies had similar outcomes, with no failures or recurrences at 4 years. Later studies have confirmed similar outcomes showing no significant variation in outcome with short or prolonged intravenous therapy for acute uncomplicated haematogenous osteomyelitis [18, 19]. It is logical, therefore, to advise 3–5 days of intravenous administration followed by 3 weeks of oral administration, monitoring the response on clinical and simple laboratory grounds. Dartnell et al.'s [6] recent review of paediatric osteomyelitis suggested that “the duration and route of antibiotic treatment are debatable” and commented that there was only one prospective randomised study on this subject.

However, the authors concluded that “in acute uncomplicated osteomyelitis a short course of intravenous antibiotics, guided by clinical and haematological parameters and followed by an early switch to oral treatment, is acceptable.” We strongly support this view.

The **second** misconception is that antibiotics must be delivered by the intravenous route for 6 weeks. This is unnecessary in patients who respond promptly to initial treatment, agreeing with Dartnell et al. that “there is increasing evidence that longer courses do more harm than good.”

Monitoring progress

Those experienced in the management of children with osteomyelitis are able to monitor progress by clinical observation. It is remarkable how quickly a sick, listless child with pain in the affected limb becomes a happy child moving around the bed after prompt effective treatment.

The child should demonstrate clinical improvement within 24–48 h and follow an uncomplicated course. Fever should settle within 2–3 days. Erythema and swelling (which should be recorded with a tape measure) should settle and the range and rhythm of movement recover. If the white cell count was elevated, it should decline within 1 week. During that time, there is usually a 20 % decline in the erythrocyte sedimentation rate (ESR) and a 50 % decline in C-reactive protein (CRP), the latter being a superior predictor. Once clinical improvement is confirmed, laboratory parameters stabilise and compliance is assured, oral medication is commenced.

It is clinical improvement which is the best guide to recovery. If the child does not show prompt improvement, the treatment is not effective. Further imaging by ultrasound or magnetic resonance imaging (MRI) should be undertaken to identify a sub-periosteal collection and give consideration to community-acquired MRSA or rarer organisms.

During the management of acute, uncomplicated osteomyelitis in infants and children, the clinical skills and experience and the willingness of the same surgeon to examine and re-examine the child frequently to monitor progress is paramount for a favourable outcome.

Once the decision has been made to discharge a patient from hospital, the frequency and type of follow-up monitoring must be determined. CRP levels, in general, fall more promptly than the ESR. It is not necessary to continue antibiotic treatment until normal levels have been reached, nor is it usually necessary to repeat MRI examinations as long as there is clinical improvement. Prolonged antibiotic administration for acute osteomyelitis is usually unnecessary [20].

Inevitably, a note of caution must be sounded. This paper addresses primary acute bone infection. When presentation is delayed, when soft tissue, sub-periosteal or intra-osseous abscesses have formed or when there is any suggestion of joint infection, different protocols should be employed. Similarly, multi-focal or sub-acute disease may dictate the need for immunological and rare organism investigation. Children's orthopaedic surgeons still see all too often cases treated incompletely by others when infection has not resolved and no organism has been identified. To complicate matters further, many antibiotics, alone or in combination, have been used for inadequate periods of time. It remains essential for children's orthopaedic surgeons to work closely with paediatricians, infection specialists and bacteriologists to minimise these risks.

Conclusion

It must be stressed that the recommendations made apply only to primary acute osteomyelitis. Joint involvement, chronic, sub-acute and multi-focal disease or an immunologically compromised child demand more complex management strategies.

The key message here is that the early diagnosis of acute primary bone sepsis should be based on suspicion, knowledge of the pathogenesis and the natural history. Appropriate imaging and haematological studies, together with prompt effective treatment, should lead to the rapid cure of a condition that was once feared. Some of our past misconceptions about disease progression and treatment have been laid to rest.

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