ACUTE HAEMATOGENOUS OSTEOMYELITIS IN INFANCY AND CHILDHOOD

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Chronic osteomyelitis is recognised as a very old disease, but acute osteomyelitis appears to have been understood only in the last 50 or so years. Until the latter part of the nineteenth century, acute osteomyelitis was only rarely recognised, except as a complication of open fractures or local sepsis.

According to Wilensky (1927) the term osteomyelitis was probably coined by Nelaton in 1844. Acute osteomyelitis has always been a serious disease because of the risk to the life of the patient as well as its tendency to chronicity and recurrence. Recent improvements in surgical care and chemotherapy have made it less formidable, but as Gilmour (1962) stated “few diseases remain unchanged over the years”. The pertinent articles of 50 years ago (Starr 1922; Wilensky 1934; Crossan 1938) are now largely of only historical interest as a result of antibiotic therapy. The unpleasant complications of the past occur much less frequently, but are still seen, particularly when the disease has been underestimated or not recognised.

Attempts at understanding the disease began a century ago when Rodet reported to the Academy of Sciences in Paris in 1884 his experimental production of haematogenous osteomyelitis in animals by means of the intravenous injection of staphylococci. In a classical paper on experimental osteomyelitis, Lexer (1894) injected measured doses of cultured Staphylococcus aureus into the veins of young animals and found that it was possible, by traumatising a given bone shortly afterwards, to cause a focus of suppuration to appear at that site.

Many of the questions which still remain unanswered about this disease were asked by Hobo (1921) who provided a satisfactory explanation for the specific localisation of bacteria in the metaphyses of long bones. His descriptions of the vasculature of growing longbones, although not the first, have been accepted and perpetuated in most subsequent reports of the pathogenesis of acute haematogenous osteomyelitis, and form the basis for Trueta’s “three types of osteomyelitis” (1959). Indeed, Trueta reproduced Hobo’s original diagram in this classic paper which related the osteomyelitic syndromes of infants, children and adults to the supposed differences in the blood supply of metaphysis and epiphysis in the three age groups.

It was not until 1979 that Ogden provided definite histological support for an initial metaphyseal focus in human neonatal osteomyelitis. The blood supply of the metaphysis and growth plate has been clarified by Howlett (1979) and recent studies in our laboratory have documented clearly the histology and changes in circulatory pattern in the natural history of acute staphylococcal haematogenous osteomyelitis in the chicken (Emslie, Ozanne and Nade 1983; Emslie and Nade 1983).

Osteomyelitis that follows direct bone injury and acute haematogenous osteomyelitis are, for practical therapeutic purposes, dissimilar lesions. The principles laid down by Winnett Orr (Connolly 1982), used with great success in the treatment of open fractures, were much less successful in acute osteomyelitis of haematogenous origin. Before the introduction of sulphonamides and antibiotics, acute haematogenous osteomyelitis had a mortality of 20 per cent and a morbidity of 50 per cent (Trueta 1968). Kennedy (1944) found that the mortality dropped from 23 per cent to 3.5 per cent with the introduction of chemotherapeutic agents. During the last 40 years, in modern communities, that figure has dropped almost to zero.

Mitchell (1938) first reported the use of sulphonamides, and penicillin was first used by Trueta in 1941. Despite these remarkable advances, Bick, in 1941, warned that “in the treatment of haematogenous osteomyelitis, chemotherapy is not a substitute for surgical judgement, operative technique or meticulous aftercare”. It had then become apparent (Hoyt, Davis and Van Buren 1941) that some cases, particularly those diagnosed early and caused by organisms of low virulence, could be treated without operation. This marked the beginning of the era of controversy regarding the role of surgery in this disease.

In addition to the introduction of antibiotics, which have changed the natural history of the disease, there have been: improvements in the techniques by which diagnosis might be confirmed, particularly in those of applying “nuclear medicine” to bone-imaging (Kirchner and Simon 1981); some statistical information regarding the outcome of primary management (Gillespie and Mayo 1981); and microbiological monitoring of causative organisms and their sensitivity to antibiotics (Nade 1977).
Many of the controversial issues in the management of this condition have arisen because the natural history of the untreated condition has not been properly understood; because alternative therapeutic regimens to those empirically initiated and perpetuated have not been adequately tested; and because most follow-up studies have dealt with small numbers of patients over relatively short periods of time. The testing of some hypotheses in the laboratory has been hampered by the lack of an experimental model; attempts to reproduce the studies of Rodet (1884), Lexer (1894) and Hobo (1921) have been unsuccessful (Hamblen 1968) and the often-quoted model of Norden (1970) is inappropriate as it mimics chronic and not acute osteomyelitis.

It is the purpose of this review to analyse the available data and debate the controversial issues, a task that does not appear to have been attempted since the publication by Waldvogel, Medoff and Swartz in 1970.

THE OCCURRENCE OF THE DISEASE
In developed communities, acute osteomyelitis is uncommon. Gillespie and Mayo (1981) reported the first 30-year period after the introduction of penicillin into civilian practice in the North Island of New Zealand (1947 to 1976) and were able to collect 655 cases from two major referral centres in that island (22 cases per year). The incidence in large Australian cities is of the same order.

In developing countries, the disease is still a major problem and chronic osteomyelitis still exists. Whether the seasons influence the incidence or there is a variation in different ethnic groups within a population, or whether both factors reflect host–parasite relations is unknown (Trueta 1968; Gillespie 1979). In areas of high prevalence there may well be a case for carrying out careful sociomedical studies.

The disease affects all age groups and was found to be most common in those aged 10 to 11 years by Trueta (1968), 9 to 10 years by Blockey and Watson (1970), 5 to 6 years by Gilmour (1962) and under one year by Nade, Robertson and Taylor (1974). The morbidity appears worse in the lower socio-economic groups.

In virtually all reports it was noted that boys were affected more than twice as often as girls. All bones have been involved (Jaffe 1972), but the most commonly affected are the femur and the tibia. In the infant and child the metaphyseal portion of the bone is most commonly affected initially.

Spread from this region into the epiphysis, although uncommon, may occur (Trueta 1959; Ogden 1979). More common is damage to the physis (although often without significant growth disturbance) and spread into adjacent joints causing septic arthritis. This is most frequent in the hip and shoulder.

The explanations for such spread demand a review of the peculiar vascular arrangements of growing bone.

THE BLOOD SUPPLY OF BONE AND ITS RELATION TO PATHOGENESIS
In the child. The medulla of the diaphysis and metaphysis in the child is supplied with blood from the nutrient artery. The epiphysis receives its blood supply by a separate route (Trueta and Morgan 1960).

Should blood-borne bacteria lodge in the vessels of the metaphysis and become established, a rather special circumstance of inflammation takes place between the bony columns which are forming. There is no room for expansion between these rigid walls and the swelling of acute inflammation leads to thrombosis of nutrient vessels.

Oedema in the area is said to force fluid and organisms through haversian and Volkmann’s canals and “lift” the periosteum, thereby interfering with vascular connections to the cortex. That is, the inner cortex becomes ischaemic because of thrombosis of the nutrient artery, and the outer cortex becomes ischaemic by virtue of periosteal lifting. The cortical bone dies, leading to formation of a sequestrum if the inflammatory process is allowed to proceed (Trueta 1959).

Although the disease almost always commences in the metaphysis, primary subacute epiphyseal osteomyelitis does occur (Green, Beaufchamp and Griffin 1981) and may have a similar pathogenesis. The epiphysis and the joint are normally protected from this ischaemic process by natural anatomical barriers—the growth cartilage and the joint capsule which attaches generally to its periphery. However, transepiphyseal vessels do exist.

In the infant. The umbilical cord of the newborn is a potential portal of entry for bacteria. The vascular arrangement of the bone is different from that in the child, the epiphysis and joint are often involved, and subsequent growth is frequently disordered.

Micro-angiographic radiological studies by Trueta and Morgan (1960) suggested there were vessels that crossed the growth plate, particularly in the neonate. This has been confirmed by Ogden (1979), and found in animals by Howlett (1980), and Emslie and Nade (1983) who detected bacterial colonies in these transphyseal vessels in osteomyelitis. There is no doubt that the neonatal growth plates (physes), which are well formed at birth, are not resistant barriers as classically taught.

These transphyseal vessels have a variable time of disappearance, following which the growth plate may become an effective barrier to spread of a metaphyseal abscess, and bacteria, from metaphysis to epiphysis.

The whole shaft may become involved in the inflammatory process and radiographs may show evidence of new bone—the involucrum—being laid down by periosteal activity along its length. This alteration, as opposed to the effects on the epiphysis and growth plate, is only transient and usually leaves no trace later in life. Spread into adjacent joints commonly occurs.

In the adult. Haematogenous osteomyelitis is uncommon
in the adult. When it does occur it most frequently involves the spine. The pattern of spread is different because the growth plate barrier is no longer present and joints are frequently affected. Much bone substance may be involved and fracture is not uncommon.

**BACTERIOLOGY**

Acute haematogenous osteomyelitis is a sequel of bacteremia or septicaemia. The causative organism may be obtained by culture of pus found at operation or culture of an aspirate from the affected area. If a clinical diagnosis is made, culture of an organism from the blood is usually accepted as evidence for its presence in the metaphysis. Waldvogel and Vasey (1980) argued that direct bone aspiration or surgical biopsy is still strongly to be considered in patients with negative blood cultures, although Cole, Dalziel and Leitl (1982) did not think this necessary.

Since the introduction of antibiotic therapy the positive identification of a bacterial cause has become less frequent. Where organisms are not identified, the diagnosis is made from clinical manifestations and radiological changes. *Staphylococcus aureus* has been found to be the cause in about 80 per cent of cases in most series. However, because it is not always the cause, it remains important to search for bacteria or fungi.

It is to *Staphylococcus aureus* that most attention must be directed, for in all cases where primary treatment failed (reported by Blockey and Watson 1970) it was the offending organism. This was confirmed by Gillespie and Mayo (1981). The site of entry of the organism to the blood stream often cannot be traced. In about 25 per cent of cases there is a history of a recent infectious process (respiratory, aural or cutaneous); a history of preceding minor injury is not uncommon, but its role is questionable.

The resistance of *Staphylococcus aureus* to penicillin has been increasing. Kirker (1953) reported no therapeutic failures in the treatment of acute osteomyelitis when all organisms were sensitive to penicillin. However, Hassam *et al.* (1978) did not find a methicillin-resistant strain in their hospital, perhaps a pointer to a prudent chemotherapeutic policy. Due consideration of these changes must be given when determining the appropriate antibiotic therapy.

**PATHOLOGY**

Initial changes at the site of localisation of infection have not been extensively studied in man, since the material is not ordinarily available. When the disease is fatal, specimens may become available for study, but reports are few and far between (Knaggs 1902; Ogden and Lister 1975; Ogden 1979). The inflammatory reaction in bone does not differ essentially from that in other tissues, although it is modified by the mineralised structure, and can create special problems in treatment (Lichtenstein 1970). The fate of the metaphyseal abscess resulting from this inflammatory process is dependent upon the virulence of the invading organisms and the resistance of the host. It may subside, become chronic or it may spread.

In cutaneous and subcutaneous infective foci, clinical evidence of abscess formation depends upon a finite number of bacteria per unit volume (10⁵ per millilitre). It is likely that similar quantitative factors apply in a focus of osteomyelitis.

Rheologic phenomena undoubtedly play a role in the initial metaphyseal localisation of infective foci. Emslie *et al.* (1983) found that in an experimental model, intravenous injection of bacteria in appropriate doses produced abscesses only in bony metaphyses, and in no other organs. Ogden (1979) has suggested that the incidence of infection in a particular site closely parallels the relative growth contributions of each physis and epiphysis. There are undoubtedly other factors, particularly the cellular and humoral immune competence of the host; perhaps the immaturity of the infant, particularly if unprotected by maternal antibodies, explains the higher incidence in this age group (Kuo *et al.* 1975).

Spread of the infection from the metaphysis involves bone resorption which takes place by both osteoclastic and non-osteoclastic processes. Dekel and Francis (1981) suggested that *Staphylococcus aureus* might be able to synthesise the prostaglandins that accelerate bone destruction.

In the absence of treatment, death of some of the physis and metaphyseal bone occurs after organisms lodge in the medullary vessels. This dead bone, seeded with bacteria, can then act as a permanent reservoir for bacterial growth and invasion. No antibiotic can penetrate the depth of this sequestrum, and hence cannot eradicate infection at this stage. The spontaneous or surgical drainage of pus is followed by repair, in favourable cases, through apposition of new bone. The cortex may become thickened by the newly-formed bone of the repair process. Where the blood supply has been inadequate, necrotic bone persists, as osteoclastic resorption can only take place on living bone. Small abscesses are eventually replaced by cellular or fatty bone marrow while large abscesses may be transformed into cystic cavities. The presence of residual abscesses or sequestra sets the stage for recurrent or chronic osteomyelitis.

Trueta (1968) stated that children accounted for about 80 per cent of cases and the majority had no permanent disability, while infants constituted about 7 per cent of cases and were frequently left with permanent damage and disability. Recent studies (Nade *et al.* 1974) suggest that the incidence in infancy is increasing.

In infants, and indeed in older children, the physis may be damaged, either by spread along a vessel or direct invasion. Growth disturbance of a significant degree probably only occurs if the germinal cells of the physis (adjacent to the epiphysis) have been damaged—either by ischaemia or direct chondrolysis. The amount of growth disturbance that follows is related to: the volume of physis destroyed; the location of such destruction (for
example, germinal or hypertrophic, central or peripheral); and the invasion and destruction of the epiphysis and the canal systems of its cartilage.

THE USUAL CLINICAL COURSE

Although acute haematogenous osteomyelitis presents a variety of clinical manifestations—depending on site of abscess, and nature of infecting organism—it is useful to use as a basis "the usual clinical course" of osteomyelitis in children. Trueta (1968) in his attempt to correlate the clinical features with his hypothesis of underlying pathology described three clinical stages.

Stage I. This he described as a "boil" in the bone. It produces pain which is severe, constant and described as "deep" or "in the bone" and is often not localised at the focus of infection. It is more useful to ask the child to point to the site of the pain. Tenderness, usually accurately localised, is constant in position and intensity, and is exquisite. At this stage there is no redness, no swelling, no heat, no fluctuation and there may be no loss of function; the child walks to the consulting room!

Stage II. At this stage there is pus in the medulla and the subperiosteal space. The symptoms and signs are more marked, and systemic symptoms such as malaise, fever, other aches and pains, headache and flushed facies appear.

Stage III. At this stage there is pus in the soft tissues. The signs of acute inflammation—calor, dolor, rubor, tumor and functio laesa—are now present.

However, the more common presentation of the patient these days has a different pattern, and has been described by Cole et al. (1982). Initially the child may complain that a limb hurts. Frequently, the parent ascribes this to an injury sustained at play and apart from giving analgesics, and perhaps applying a bandage, does little more. Should the discomfort persist, the local medical practitioner is often consulted. No one thinks of acute osteomyelitis. Usually, nothing is done, or, should the child be febrile, antibiotics are prescribed. On the following day, if the child is still complaining of discomfort, a consultant's opinion is obtained. Thus, the common presentation to the consultant is a child with an acute febrile illness of about 48 hours duration, limb pain and tenderness over the metaphysis of a long bone. Redness and local swelling may be present if there is extra-osseous extension of the infective process. The child resists using the limb, although with care it can be passively moved. If untreated, systemic and local symptoms worsen in most cases and there is little doubt about the presence of an abscess in the extra-osseous tissues.

Osteomyelitis of the ilium has features a little different from peripheral bone sepsis. Beaupre and Carroll (1979) described three separate syndromes associated with infection of the iliac bone—the first mimicking a lumbar intervertebral disc lesion, the second a gluteal syndrome, and the third with predominantly abdominal features.

Neonatal osteomyelitis is now more common than in the era before antibiotics (Gilmour 1962; Nade et al. 1974). The clinical presentation of acute osteomyelitis in the neonate is quite different from that in older children and is rarely recognised in the early stages. The infant usually presents with swelling of the limb and a considerable amount of pus already formed. Complete refusal to move the limb is the most pronounced sign. In other respects, the infant may be mildly unwell and not show a high fever. Careful clinical examination for the localisation of an infectious process should lead to the diagnosis. The pathology of neonatal osteomyelitis with clinical correlations has been well described by Ogden (1979).

DIAGNOSIS

The diagnosis of "classical" acute haematogenous osteomyelitis is clinical. Anderson, Scobie and Watt (1981) in reviewing 217 patients with this clinical diagnosis suggested that it should be made in children with acute local bone tenderness and a positive blood culture, or in the absence of the latter, the clinical findings of increased body temperature, local bone tenderness, local limb swelling, and at least one of the local erythema, local increase in skin temperature and decrease in range of adjacent joint movement. Any unwell infant or child with an area of local bone tenderness has osteomyelitis until proved otherwise, and should be treated as such. Because a number of different organisms may be responsible for the bone infection, it is wise to seek conclusive bacteriological diagnosis as an aid to treatment.

The yield of organisms by local aspiration is about 60 per cent; this can be augmented by saline lavage of the aspirate site. Although frequently practised for suspected septic arthritis, it is far too uncommonly done for suspected osteomyelitis.

Haematology. The erythrocyte sedimentation rate is usually raised as is the white cell count which generally shows a neutrophil leucocytosis and mild anaemia is not infrequent. However, none of these non-specific findings have any relationship to whether a subsequent operation is indicated, or to the probability of failure in treatment (Anderson et al. 1981).

Radiology. Despite the commonly quoted statement that radiology is of no use in the early stage, because bony manifestations do not appear until about 10 days, careful attention to soft-tissue shadows may reveal the diagnosis (Ferguson 1975). Usually a soft-tissue density adjacent to the bone helps differentiate acute osteomyelitis from acute septic arthritis in which there is distension of the joint, or cellulitis in which the soft-tissue density is beneath the skin and at a distance from the bone. The first radiological feature in bone is usually the presence of periosteal new bone and only later is there evidence of bone destruction, osteoporosis and sequestrum formation.

The combination of periosteal new bone formation
and a lucency within the bone is the most common radiological change, but this also occurs in neoplastic conditions. Indeed Ewing's tumour and osteomyelitis may occur together. The balance between erosion and periosteal response often serves as a key to the differential diagnosis (Simon 1965). However, the periosteal reaction is a non-specific response of this tissue to insult or injury and does not mean that bone infection has occurred.

**Radionuclide imaging.** In the last decade radionuclide imaging has improved our diagnostic accuracy: it is not, however, mandatory to use this technique if the diagnosis is already clear. As will be indicated, the early institution of antibiotic therapy is fundamental, and delays as a consequence of awaiting the results of numerous "confirmatory" tests may well be the genesis of chronic osteomyelitis. I am amazed that, often, skilled clinicians doubt their own experience and pay homage to a typewritten report provided by a department with a new machine. The scan should not be used as an excuse for a poor clinical examination! Of the many substances used for bone imaging, technetium-99m labelled methylene diphosphonate (99mTc-MDP) seems to give the best results. The mechanism of labelling diseased bone is disputed; a combination of the "blood flow phase" image (obtained within seconds of intravenous injection of the radionuclide material) and the "bone uptake" (obtained some three to four hours later) is the best way of interpreting the pathophysiology of osteomyelitis.

Despite its usefulness, radionuclide imaging has four important limitations, according to McCoy, Morrissy and Seibert (1981). First, in some patients, multiple "hot spots" are detected at an "early" stage of Staphylococcus aureus septicaemia but do not progress to osteomyelitis; they are probably areas of aborted infection. Nevertheless, scans limited to clinically suspect areas should never be done, as whole body imaging may detect sites which are not clinically suspicious. Secondly, there are numerous studies, experimental and clinical, in which osteomyelitis has been confirmed bacteriologically and histologically, even though scans were initially negative (Berkowitz and Wenzel 1980). Thirdly, radionuclide imaging sometimes does not allow the differentiation of cellulitis from osteomyelitis—especially if the early "blood pool" imaging is not done at the same study as the "uptake" image. Finally, bone scanning does not differentiate the bone repair of infection from the bone repair of fracture or neoplasm; and 99mTc-MDP scans are not useful indicators of healing or "progress".

It is important to understand the mechanics of radionuclide imaging, as the "blood pool" view is not specific for hyperaemia and there is no difference in scintigraphic findings due to cellulitis or osteomyelitis. Sullivan et al. (1980) even suggest that physical examination gives the same information about hyperaemia.

These problems are partially solved nowadays by the development of radiopharmaceuticals that are bound specifically to infected tissues. 67Ga-citrate is one such agent. It appears to accumulate in inflammatory exudates (Lisbona and Rosenthal 1977). The local accumulation of 99mTc-MDP and 67Ga-citrate in the same site in bone is highly suggestive of an inflammatory focus at that site. Serially decreasing accumulation of 67Ga-citrate, even without change in 99mTc-MDP uptake, suggests that inflammation is resolving. By performing both scans on the same day the amount of information provided may be increased. Scoles, Hilty and Sfakianakis (1980) attempted to follow the course of acute osteomyelitis by regular radio-isotope scans in 16 patients. In seven there was an increasing uptake of 99mTc-MDP for 10 to 15 days, while nine showed a maximal uptake on the first day with return to normal levels over up to 60 days. Because the time of admission to hospital and therefore scanning was so variable after onset of symptoms, the quantitative scan findings were of no value.

**Serology.** The usefulness of serological tests at present is uncertain as their sensitivities and specificities need to be better tailored for diagnostic purposes. Where facilities are available for measurement of staphylococcal antibody titres, there may be a rise in the levels of antibodies against the alpha-haemolysin. Anderson et al. (1981) found antistaphylococcal titres of less than 2 milligrams per litre in all of 97 patients tested who actually had osteomyelitis. It seems that not all laboratories perform the test in the same way. Rising titres cannot be relied upon to demonstrate a staphylococcal source of infection. In acute osteomyelitis (with septicemia) simple tests, as described, are much more useful.

Harris and Kirkaldy-Willis (1965) described a primary subacute pyogenic osteomyelitis and in doing so questioned the existence of the rare condition, described by Garré in 1893, of sclerosing non-suppurative osteomyelitis. Primary subacute pyogenic osteomyelitis is more common than the acute form in East Africa; there is no acute febrile illness, the onset is insidious and there is no general reaction. In patients suffering from sickle cell disease the shaft is more commonly involved than the metaphysis, there is often more than one focus of infection and quite frequently the invading organism is a salmonella (Adedayo-Kunnu and Hendrickse 1980) which can frequently be grown from the faeces.

**THE PRINCIPLES OF TREATMENT**

It was noted by Wakeley as early as 1932 that the incidence of acute osteomyelitis in children was decreasing, and he suggested that the disease might disappear because of improved nutrition and increased resistance to infection. During the following decade, chemotherapy emerged as a most powerful weapon against infectious disease, and until about 1951, when penicillin-resistant staphylococci evolved, nearly all cases of acute haematogenous osteomyelitis were treated without surgical intervention. With the emergence of strains of bacteria resistant to antibiotics there has been an increasing incidence of the disease, with some failures of treatment.
The following five principles of treatment are suggested. First, the appropriate antibiotic is effective before pus has formed. Secondly, systemic antibiotics cannot sterilise avascular tissues and pus, which should therefore be removed. Thirdly, if such removal is effective, systemic antibiotics can prevent their further formation; therefore primary suture of skin is safe. Fourthly, bone is damaged by ischaemia; therefore, surgery, if performed, should not put at further risk the already ischaemic bone. Pus removal aims at restoring continuity between the periosteum and the cortex, and allowing intramedullary flow. Finally, antibiotic therapy should be continued after surgery.

The three main areas of debate concerning management of patients with acute haematogenous osteomyelitis are over which antibiotic to choose, the value of early operative intervention, and the duration of treatment; (“If osteomyelitis is to be treated conservatively it should be by an orthopaedic surgeon who is prepared to intervene at once and operate if that is indicated”; Blundell Jones 1971).

The surgeon responsible for the care of the child should examine him on admission. A careful clinical assessment is made and a blood sample obtained for the tests mentioned above. Any septic lesion is swabbed, or aspirated, and as well as commencing a culture from it, a Gram’s-stain should be performed to obtain some indication as to the organism present. At this time it is not known whether surgery will be necessary, nor when. The ill child may not have eaten for many hours and may have vomited. Therefore, the intravenous route is used for rehydration and this also serves as a route for administering antibiotics. Immobilisation of the affected limb should be maintained, but this does not necessarily mean the application of a cast or splint in the acute and very painful stage. As protective muscle activity prevents movement, resting the limb on a pillow may be sufficient, and also allows for frequent examination of the limb. A shaped cast or splint often makes nursing of the patient a less demanding procedure.

In this way the patient is prepared for surgery should this become necessary.

WHICH ANTIBIOTICS SHOULD BE USED?
The antibiotics should be appropriate in type and dose. Nowadays the majority of infections are due to *Staphylococcus aureus*, although Green and Shannon (1936) demonstrated that in infants less than one year old streptococci were the most common organisms isolated. Since that time, streptococci seem to have decreased in virulence and produce less therapeutic problems than staphylococci, although it has recently been reported that group B streptococci were the single most frequent organism associated with osteomyelitis diagnosed in the first two months of life (Edwards et al. 1978; Memon et al. 1979).

It is not possible in all cases to identify the infecting organism or determine its antibiotic sensitivity; this may be a result of administration of antibiotics before blood cultures are taken, failure to obtain blood cultures, the decreased incidence of operative intervention or failure to grow organisms from various specimens obtained. Organisms have been grown from clinically diagnosed cases of haematogenous osteomyelitis in about half to two-thirds of the patients treated (Winters and Cahen 1960; Meyer, Kieger and Smith 1965; Blockey and Watson 1970; Nade et al. 1974; Anderson et al. 1980). The author has found that the yield was usually higher if surgery was performed, suggesting that antibiotics given before operation had not sterilised the pus.

The isolated and presumed causative organism in over 80 per cent of cases studied in the antibiotic era was *Staphylococcus aureus* (Gilmour 1962; Green 1967; Blockey and Watson 1970; Anderson et al. 1980; Cole et al. 1982).

Green (1967) also pointed out the increasing rate of therapeutic failure as resistance of organisms to penicillin appeared and increased. Blockey and Watson (1970) found that there were no therapeutic failures in cases in which the organisms were other than staphylococci, and Gillespie and Mayo (1981) found only one out of 123 failures to be *Streptococcus pyogenes*—the rest were *Staphylococcus aureus*.

Gillespie and Mayo (1981) found organisms in 63 per cent of patients; the isolation rate was 9 in 10 in patients classed as failures of primary management while it was only 5 in 10 patients classified as successes. Similarly, Cole et al. (1982) isolated *Staphylococcus aureus* in 11 out of 12 patients classified as late-acute osteomyelitis.

However, Blockey and McAllister (1972) stated that a possible increase in *Haemophilus influenzae* infections was a cause of concern in view of the fact that a subsequent study showed some failures when this was the invading organism. Schwartz and Reing (1981) have also drawn attention to the increasing incidence of this organism in infants.

The choice of antibiotic therapy should therefore be dictated by the above principles. Bacteriocidal antistaphylococcal antibiotics should be administered parenterally in adequate dose. Not surprisingly, Gillespie and Mayo (1981) found that the use of a bacteriocidal antibiotic, rather than a bacteriostatic one was associated with a significantly smaller rate of failure. In addition, it would appear to be reasonable to administer simultaneously an antibiotic effective against streptococci. The critical question, however, is should all cases be treated as if they were due to *Staphylococcus aureus*, that is with cloxacillin alone, or should they be treated with a combination of antibiotics to cover more organisms?

If a combination of antibiotics is to be used initially in treatment, the choice can, and does, change depending upon the changing spectrum of causative organisms, and their antibiotic sensitivities. This requires continuous
monitoring, and is something which can be easily subjected to computerisation, as has been observed in our unit and shown by Cole et al. (1982).

Examination of hospital records by Buckle and Williams (1978) showed that two or three drugs were often used, and often changed, not necessarily in accord with the results of sensitivity tests. The fact that results of treatment are not as good as they should be appears to stem from this indecision.

Should the suspicion of acute osteomyelitis be aroused, blood should be drawn for bacteriological culture and parenteral antibiotics administered immediately.

The combination of cloxacillin and penicillin has been recommended by several authorities (Blockey and Watson, 1970; Meyer et al., 1965; Nade, 1978; and Cole et al., 1982). Blockey (1971) and Blockey and McAllister (1972) subsequently advocated a combination of sodium fusidate and erythromycin instead of their previous recommendation of benzylpenicillin and cloxacillin. Although they were unable to culture Staphylococcus aureus from a child with acute osteomyelitis resistant to cloxacillin or methicillin, they suggested that organisms resistant to those drugs might be emerging. Methicillin-resistant Staphylococcus aureus is now a serious problem in nosocomial infections, but, to date, has not been found to any significant extent in haematogenous osteomyelitis.

Sodium fusidate and erythromycin are drugs of low toxicity, show synergism and broaden the range of antibiotic coverage (for instance, to include Haemophilus). As the evidence to support the use of these two drugs is not convincing this combination is not recommended as the first choice.

The author’s practice is essentially the same as that detailed by Cole et al. (1982) in this journal. Cloxacillin (100 to 200 milligrams per kilogram of body weight, taken daily in divided doses) by the intravenous route is used for as long as such a mode of administration is necessary—not usually more than 72 hours. It is ceased when the child is clinically well, has no fever and the local signs have decreased. When oral therapy is instituted, the form of drug is changed to flucloxacillin, at half the dose level for cloxacillin, given between meals. This is important because of the effect of gastric contents on absorption of this drug. The level of dose by mouth is controlled initially on a body weight basis (50 to 100 milligrams per kilogram of body weight, taken daily in divided doses), but adjusted on peak and trough serum levels to provide a level in excess of the minimal inhibitory concentration for the causative organism, or a maximum of 20 micrograms per millilitre if no organism is grown.

Although the clinical response can be used for determining the antibiotic dose, when oral therapy is used it should be monitored by measurement of not only the serum concentration but also the serum bacterial titre (Kolyvas et al., 1980) performed by tube dilution methods. Peak titre should be at least 1:8 (Prober and Yeager, 1979). If less than this, probenecid (10 milligrams per kilogram of body-weight, taken daily) should be added to oral therapy. The sensitivity of discs to antibiotics on a culture medium is not thought good enough for infections of bone (Septimus and Mushet, 1979).

In addition benzylpenicillin should be given intravenously (0.25 to 1.0 million units every six hours) for as long as the intravenous route is necessary. When replaced by oral administration, phenoxymethylpenicillin is given in a dose of 100 milligrams per kilogram of body-weight in divided doses at six-hourly intervals.

If an organism is isolated the single effective antibiotic is given; if no organism is isolated both flucloxacillin and penicillin are given.

If the child is intolerant of penicillins, then a cephalosporin such as cephradine or cephalaxin can be given at a dose of 100 milligrams per kilogram of body-weight taken daily, intravenously or orally.

In their authoritative book Buckle and Williams (1978) suggested several suitable drugs of which methicillin, cloxacillin, benzylpenicillin, lincomycin and chloramphenicol are the most important. They recommended that treatment should be “in the great majority of cases a fairly large dosage of one of these... continued for a number of weeks, even when a prompt clinical response is obtained”. The recommendations of Cole et al. (1982) from the same hospital are more specific and should be followed in preference. There is no place for broad spectrum antibiotics, and lincomycin (McMillan, McRae and MacDougall, 1967) appears to increase the risk of pseudomembranous colitis.

**IS SURGERY NECESSARY?**

The author’s indications for surgery are as follows: the presence of an abscess, as judged clinically; the clinical diagnosis of osteomyelitis in a child who is severely ill; and an inadequate initial clinical response (that is increased local tenderness and swelling and failure to see a fall of temperature between any two examinations after commencing treatment). The assessment of clinical improvement is made by examination of the patient, the involved limb and the fever, which one would like to see subside markedly within a short time of commencing therapy. Other indicators of progress, from the haematology laboratory or organ imaging department, change towards normal over days and weeks, and are no guide at an early stage.

Contraindications to surgery are a child with a bleeding disorder (unless haemostasis can be assured), probable high morbidity from the surgical approach (for example, as in cases of pelvic sepsis) or parental refusal.

In the acute phase, the major decision is whether surgical intervention is indicated. Incision of abscesses has been practised since time immemorial. William Hey (1810) recommended enlargement of spontaneous fistulae and removal of dead bone. Starr (1922), Lexer (1897),
Wilensky (1927, 1934) and others stipulated early drainage by incision of the periosteum, drilling of the cortex, cutting "windows" in the cortex or "wide saucerisation" of diseased bone. The surgical resection of diseased bone in toto was practised in nineteenth century France and required subsequent surgical treatment of unsightly bony defects.

The question of operating early or waiting for localisation of pus was hotly debated in the era before chemotherapy. In the 1920s most surgeons believed that early incision was not injurious, while late incision was an invitation to fatality. In the following decade, emphasis was placed on localisation of the abscess. Crossan (1938) and Wilson and McKeever (1936) before antibiotic drugs, and Nachlas and Markeim (1948) using penicillin, found that immediate surgery, in an attempt to avoid bone destruction, produced only an increase in mortality. This may have been related to inadequate resuscitation of the patient and Gilmour (1962) stated that surgery has no place in treatment during the acute septicaemic phase of the illness. Blockey and Watson (1970) questioned the value of early surgery which has been claimed to "release tension", prevent death of cortical bone, decrease the likelihood of further spread of infection and allow identification of the affecting agent. They concluded that operation should be reserved for those with infections in which an abscess was clinically detectable. A scar on a child's limb seemed too high a price to pay for bacteriological certainty and they selected antibiotics on a "best guess" principle. The debate regarding surgery still rages.

Controlled studies evaluating the effectiveness of surgical approaches are rare, and Waldvogel and Vasey (1980) declared that surgical treatment of osteomyelitis is largely empirical, and based on concepts that have gained wide acceptance—some with, and others without scientific documentation.

Indeed, the natural history of acute osteomyelitis, in an experimental model, in the antibiotic era has for the first time been revealed by Emslie and Nade (1983).

The thorough study by Gillespie and Mayo (1981) indicated that 80 per cent of patients with acute haematogenous osteomyelitis were cured by primary treatment (antibiotics, immobilisation, and general support). In their analysis of failures of primary treatment (20 per cent), there was a significantly higher number treated by antibiotics and operation than by antibiotics alone! This study in a large population of cases disputes the conventional teaching that early intervention gives fewer complications—indeed, even the early introduction of antibiotic treatment may not be as important in the eventual outcome as has been thought. Certainly, it is inescapable to deny that the rate of failure was higher in those children subjected to surgery—a form of treatment advocated for all children by Mollan and Piggot (1975). Cole et al. (1982) also demonstrated clearly that non-operative treatment was curative in 78 per cent of patients. The view of Mollan and Piggot cannot, therefore, be supported.

The essential problem in the evaluation of surgical treatment is the lack of clear and specific indications for it. There is no doubt that a carefully controlled prospective clinical trial is justified to clarify the issue.

Should operative surgery be indicated, it should be performed with a pneumatic tourniquet on the affected limb; using an incision centred on the point of maximum tenderness; to allow release of pus in the soft tissues and beneath the periosteum; and by excising dead soft tissue, but without removal of bone.

The virtue or need for the drill holes has not been confirmed, as quite frequently no purulent material is obtained through them. Drill holes may allow a decrease in intramedullary pressure in the metaphyseal region and thereby allow an improved blood flow. This also has not been tested. Some believe that if no subperiosteal abscess is exposed and there is no soft or irregular cortical bone which gives way, leading into a deep abscess, then a drill hole should be made in the cortex, but this is perhaps a traditional form of surgery, lacking the support adduced for not drilling by Cole et al. (1982).

Most now advocate closed suction drainage, but its value has neither been proven, nor even compared with the results without drainage.

The limb should be immobilised in such a way that the wound can be inspected. Aspiration of pus in the soft tissues, on one or more occasions, together with antibiotic therapy, has been advocated, but has little to recommend it, and it is suggested that should the need arise the wound should be reopened, irrigated and further evacuated.

Antibiotic therapy has transformed acute osteomyelitis into a disease which may not even require surgical intervention, or if pus must be evacuated, will allow natural healing.

**THE DURATION OF ANTIBIOTIC THERAPY**

Trueta (1968) recommended prolonged antibiotic treatment of patients with acute osteomyelitis, for example, six weeks of full dosage because inadequate duration of treatment could be expected to increase the incidence of reactivation. The length of treatment appears to be empirical and Blockey and Watson (1970) attempted to determine what period might be considered adequate. They selected a period of 21 days for patients with specific radiographic bone changes and 10 days for others. As a result of their study, they recommended that after 10 days it would be reasonable to discontinue antibiotic therapy if the clinical signs had subsided, the erythrocyte sedimentation rate was normal or falling, and a radiograph showed only local osteoporosis without erosion of the cortex or new bone formation. In those who did not satisfy these conditions, a reassessment was made at 21 days, and if the clinical state was satisfactory, with no bone tenderness and a range of painless movement, antibiotics could be discontinued. They
recommended that a raised erythrocyte sedimentation rate should be ignored if it was declining. Cavities, erosion and new bone formation in the third radiograph, should also be ignored if there was no bone tenderness and if the limb could be moved without pain. A comparable study that has been done to test these recommendations is that of Gillespie and Mayo (1981).

Their was not a trial, but a retrospective review of case records. Because of the large number of patients involved (655 in all) statistical analyses were valid. They concluded, on the basis of no significant difference in failure rates, that “three weeks, or even less, of antibiotic, whether parenteral or oral, may be sufficient” and suggested that their findings justified the organisation of a prospective clinical trial. No such trial has ever been reported and this author, while practising what they suggest, would support the proposal of a trial. The “feeling” of Anderson et al. (1980) that antibiotics should be continued for six weeks is no more than a “feeling” and cannot be accepted without question. Of more value is the study of Cole et al. (1982) who reported the experiences at the Royal Children’s Hospital in Melbourne, where a six week protocol of therapy was followed in 75 patients.

Furthermore, Gillespie and Mayo (1981) found that contrary to conventional teaching that antibiotics should be instituted within the first 10 days, delay from onset of symptoms to antibiotic administration did not significantly affect the outcome in 613 children. Nonetheless, early diagnosis and prompt antibiotic therapy must be supported on the basis of the experimental findings of Emslie and Nade (1983) and the study of Cole et al. (1982).

Whether the child should remain in hospital is another factor. Compliance with adequate oral treatment regimens is often poor, and Septimus and Mushar (1979) stated that because of this hazard, children should remain in hospital to ensure oral antibiotic ingestion and adequate blood levels. The Melbourne experience of Cole et al. (1982) indicates that prolonged hospitalisation is unnecessary once the parents and child have been instructed in how to administer antibiotics by mouth.

The role of antibiotics in the eradication of this disease remains unclear. They certainly cause systemic improvement in the child. However in the respect of histological changes recent studies by Emslie and Nade (1983) in an experimental model suggest that the antibiotics do not influence the abscess at all. The animals improved in general health, but the histological changes in the metaphysis continued. The survival of the animals allowed natural defence mechanisms to operate and abort, or heal, foci of infection—and raise the question of the stimulation of natural defence mechanisms by immunogenic stimuli in the future management of this disease. This issue has also been raised by Adeyokunnu and Hendrickse (1980) in respect of osteomyelitis due to Salmonella.

COMPLICATIONS

Death rarely occurs in acute haematogenous osteomyelitis today, and it is usually the result of an overwhelming septicaemia with involvement of several organs, particularly the lungs.

The risk of chronic osteomyelitis remains a major reason for seeking to improve the rate of cure of acute haematogenous osteomyelitis. If the child presents early enough, and the principles of treatment are followed meticulously, chronic osteomyelitis should disappear. Surely, the reduction of the volume of sequestrum to a minimum is the fundamental means of preventing its occurrence.

Another complication is aberration of growth. Whether the function of the growth plate is retarded or accelerated depends upon the effect of the metaphyseal infection on the germinal cells at the epiphyseal edge of the growth plate.

Gilmour (1962) stated that overgrowth is a normal sequel of acute osteomyelitis. Roberts (1970) followed a series of patients who had osteomyelitis in infancy through to adolescence and found that there was some shortening of the affected limb in every case. Unequal growth has clinical significance only if it is considerable, and affects only a portion of the growth plate, producing an angulatory deformity, or affects one of a pair of bones (in the forearm or leg) producing a curve in the limb. When deformity of the contour of a bone, often seen radiologically, is a result of irregular laying down of bone during the repair process, it does not produce significant clinical deformity.

Involvement of an adjacent joint leads to suppurative arthritis, particularly in the shoulder or hip as the metaphysis of the humerus and femur respectively are intracapsular. This is seen more frequently in infants; in this age group the growth plate has some anatomical variation from children, especially transphyseal vessels (Ogden 1979).

Local extension into adjacent soft tissues may occur in untreated cases, with spontaneous discharge of pus through the skin. The process of resorption of bone either in the acute phase or more often as the disease is becoming chronic, may lead to pathological fracture.

Other interesting findings by Gillespie and Mayo (1981), with regard to outcome, were the risk of recurrence, and the site of the infection. They found that the risk of recurrence fell rapidly as the number of months increased after onset. If the overall recurrence rate is 20 per cent then a child who has had no recurrence by six months has only a 6.8 per cent chance of further trouble, and if no recurrence by a year, only a 3.6 per cent risk of further problems remains. Such figures are of value in counselling the patient and parents.

With regard to site of infection, 50 per cent of metatarsal foci were classed as failures (recurrence), between 20 per cent and 30 per cent for upper and lower
tibia, and lower femur, while the lower fibula, upper limb bones, and spine were not associated with failure.

PROGNOSIS

Acute haematogenous osteomyelitis is now a curable disease. The chance of cure is directly related to the following five factors: first, the virulence of the organism causing the infection, and the resistance of the host to the spread of that infection; secondly, the choice of antibiotics used initially—these should be the bacterioidal antibiotics most appropriate in treating staphylococcal infections, given parenterally in adequate dosage; thirdly, the site of infection; fourthly, the duration of treatment with antibiotics; and finally, a short interval between onset of symptoms and institution of correct therapy.

The behaviour of acute haematogenous osteomyelitis is very variable and considerable clinical judgement and experience is necessary in its management. Delay in instituting proper treatment, persistence with conservative treatment, and inadequate surgery, are the factors which lead to bad results in this curable disease.

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ACUTE HAEMATOGENOUS OSTEOMYELITIS IN INFANCY AND CHILDHOOD