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Acute Hematogenous Osteomyelitis in Children

Recognition and Management

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Contents

Abstract

Acute hematogenous osteomyelitis is most common in children and has the potential to cause life-long musculoskeletal deformities. Most cases are caused by *Staphylococcus aureus*. *Haemophilus influenzae* type b (Hib) is now rare in countries that routinely use the Hib vaccine. Although magnetic resonance imaging is the preferred modality in localized disease, scintigraphy is often preferred as the first line of investigation because it helps to clarify the location of infection and exclude the presence of multifocal disease. Where the presentation is typical, there is no underlying disease, there is a low prevalence of community-acquired methicillin-resistant *S. aureus* (CA-MRSA), and there is a good response to antibacterial therapy, a diagnostic bone aspirate or biopsy is not necessary. The first-line antibacterial choice in most circumstances is a β-lactamase-resistant penicillin. If CA-MRSA is suspected, the first-line options include clindamycin, the addition of an aminoglycoside or, rarely, vancomycin. In most patients, the total duration of therapy can be substantially shorter than the traditional 6 weeks, and oral therapy can be commenced after a brief course of intravenous antibacterials. We recommend 3 days of intravenous therapy followed by 3 weeks of high-dose oral antibacterials, provided there is no underlying illness, the presentation is typical and acute, and there has been a good response to treatment initially. Any deviation from this requires more intensive confirmation of the diagnosis (with imaging and/or biopsy or

aspiration), and prolongation of intravenous therapy and total duration of treatment. Close monitoring and follow-up for at least 2 years are advised to detect complications.

Acute hematogenous osteomyelitis (AHOM) is a serious pyogenic infection, usually caused by bacteria and most commonly found in children. Although usually curable with antibacterials and the judicious use of surgery, the potential complications of AHOM in childhood are severe. Infection and destruction of physeal cartilage can lead to growth arrest and deformity, which may be amenable to new surgical reconstruction and limb-lengthening techniques, whereas damage to articular cartilage can lead to permanent joint disease that is usually irreversible. Clinicians must remain vigilant in recognizing this disease, and ensure timely and complete treatment.

In recent years, some aspects of the management of AHOM in children have changed. Immunization against *Haemophilus influenzae* type b (Hib) in many countries has reduced the need for antibacterial coverage of this organism. The diagnosis of AHOM is now more reliant on imaging techniques including scintigraphy, ultrasonography, and magnetic resonance imaging (MRI). The role of early aspiration is increasingly questioned. Parenteral-oral sequential therapy has become standard, and the duration of both the parenteral and oral components of the treatment regimen has been shortened in selected patients. Response to treatment is monitored clinically and with evaluation of the C-reactive protein (CRP), while the use of antibacterial and serum bactericidal level measurements is controversial. This article addresses all of these issues. It does not, however, address in detail the topics of subacute or chronic osteomyelitis.

1. Definition

AHOM is an infection of the bone that is of rapid onset after blood-borne pyogenic organisms settle in the metaphysis.[1,2] By convention, AHOM is differentiated from chronic osteomyelitis based on the duration of symptoms and/or signs (<14 days is considered acute), and the absence of other features indicating chronicity (e.g. radiologic changes other than periosteal elevation or soft tissue abnormalities at presentation suggest chronic disease).

Subacute osteomyelitis is a separate entity in which the evolution of bone infection is slow and diagnosis is delayed – one study found that the average time from onset of symptoms to diagnosis was 12 weeks.[3] It is diagnosed by histologic appearance, particularly as the main differential diagnosis is bone tumor.[4] Subacute osteomyelitis was originally described by Brodie in 1836 as a metaphyseal abscess and, since that time, a number of subtypes have been described.[3]

Chronic osteomyelitis is characterized by bone necrosis with the clinical features of persistent or recurrent infection with pain and fever.[5] It may develop as a complication of AHOM if that is inadequately treated, or more commonly as a consequence of nonhematogenous osteomyelitis such as a complication of surgery or after major trauma. It is difficult to manage and may require repeated surgical debridement and prolonged antibacterial therapy.

2. Pathogenesis

A number of anatomical features make the growing bones of children particularly susceptible to infection with blood-borne organisms. Children's bones have a rich blood supply to the metaphysis via nutrient arteries, but relatively slow blood flow through capillary loops and sinusoidal veins at the metaphyseal-epiphyseal junction.[6-8] These vessels have a poorly developed reticuloendothelial system.[9] Therefore, this slow-flow area allows bacteria to deposit and replicate while protected from host defenses. *Staphylococcus aureus* has the further ability to adhere to bone by expressing receptors (adhesins) for parts of the bone matrix.[10-12] An inflammatory response ensues that is mediated by cytokines leading to the accumulation of pus under pressure, which further occludes the microvasculature. The increased stasis and activity of cytokines encourages clots to form in these vessels, leading to ischemic bone necrosis. Infection then spreads laterally through the Volkmann canals and Haversian system into the cortex and then into the subperiosteal space, causing subperiosteal abscess formation.[6,7]

Progression to chronic osteomyelitis is characterized by necrosis and the development of sequestra.[13] Ischemic bone necrosis can lead to an area of cortical bone that is deprived of its medullary and periosteal blood supply – this is a sequestrum. This bone becomes separated from normal bone, remains dense, and does not demineralize like healthy bone. An involucrum is reactive periosteal, new living bone that surrounds the dead bone. The formation of sequestra can lead to segmental bone defects and pseudarthroses. A Brodie abscess is a subacute, well demarcated focal infection that is walled off by granulation tissue that forms a fibrous capsule; these abscesses generally form in the metaphysis.

Extension of infection into the adjacent joint space (leading to septic arthritis) is more common in children than adults, and particularly in the neonate, possibly because of transphyseal blood vessels that can transport bacteria from metaphysis to epiphysis.[7,8,14] However, this theory is contested by some.[15] Neonatal bones also have a thin, poorly formed cortex and periosteum and so are at increased risk of spread to muscle and skin. Children are also at a higher risk of concurrent septic arthritis if they have AHOM that involves a bone where the metaphysis is intra-articu-

lar. These joints are the proximal femur, proximal humerus, proximal radius, and distal lateral tibia.[16]

3. Epidemiology

The overall annual incidence of AHOM in children in more developed countries is probably around 1 in 5000.[6] As with many infectious diseases, the incidence of AHOM is much higher in Aboriginal children in Australia and Maori children in New Zealand than children of other ethnicities in these countries, at approximately 1 in 800 per year.[17] The epidemiology is not well described in less developed countries, but AHOM is likely to occur at a similar frequency to these indigenous populations. Approximately 50% of cases of AHOM occur in children under the age of 5 years, and of these 25% are under 1 year of age.[15,18,19] AHOM is less common in adolescent children,[20] becomes relatively rare in middle adulthood, but then peaks again in the elderly where it is often caused by Gram-negative bacilli.[10] AHOM is more common in boys than girls – in most studies by a ratio of 2 : 1.[21-24] This may be due to increased incidence of trauma in boys. Patients with hemoglobinopathies such as sickle cell disease and immunocompromised patients are at higher risk of AHOM than the general population.

4. Microbiology

S. aureus causes the vast majority of cases of AHOM. The positive culture rate from combined blood and bone culture in most series ranges from 20% to 90%[22,25] and *S. aureus* is generally responsible for over 80–90% of these culture-positive cases.[18,23,26-28] The remaining 10–20% of culture-positive cases are caused mainly by group A streptococcus, Hib, *S. pneumoniae*, *Pseudomonas aeruginosa*, Gram-negative enteric organisms, group B streptococci, and other more rare organisms.

Older series quote Hib as a cause of 2–12% of AHOM, particularly in younger children.[18,25,29,30] The most comprehensive study reviewed all patients with osteomyelitis at one hospital over a 28-year period from 1959 to 1986 and found that Hib was responsible for 4.4% of cases.[31] However, the introduction of the Hib conjugate vaccine in most industrialized countries has led to the virtual elimination of invasive disease caused by Hib in these settings,[32,33] although cases of invasive Hib do still occur.[34] Hib remains an important cause of AHOM in regions where the Hib vaccine is not available, mainly in less developed countries.

Group A streptococci are particularly associated with concurrent or recent varicella infection.[35] *S. pneumoniae* is most commonly found in children under 2 years of age.[36] *P. aeruginosa* is almost exclusively found in immunocompromised children or when there is a history of penetrating injury to the foot, classically caused by stepping on a sharp object such as a nail while wearing a running shoe. In these cases the patients are generally older than those with staphylococcal disease, inflammatory markers may not be raised, the calcaneus is commonly affected, and the clinical course is more protracted requiring prolonged antibacterial therapy and often surgical debridement.[29,37-39] Some rarer organisms are becoming more common in some parts of the world, including *Kingella kingae*, which is particularly common in children under 2 years of age.[40]

Patients with sickle cell disease are at high risk of developing serious bacterial infections, and AHOM is particularly common, probably because of relative ischemia caused by microinfarctions. Although *S. aureus* is still the predominant organism,[41] almost as many cases in these circumstances are caused by *Salmonella* spp.[42] Other Gram-negative organisms should also be considered.

S. aureus remains the predominant organism in neonatal osteomyelitis, but most other cases are caused by the same organisms that cause neonatal sepsis, namely group B streptococcus, *Escherichia coli*, and other Gram-negative organisms.[43,44]

Although AHOM is usually caused by methicillin-susceptible *S. aureus*, the incidence of community-acquired methicillin-resistant *S. aureus* (CA-MRSA) has been increasing in many countries since the first cases were described in the mid-1980s.[45] In fact, the first reported case of CA-MRSA in a child occurred in a 6-year-old boy with osteomyelitis in 1995.[46] A New Zealand study of 130 children admitted with musculoskeletal infections caused by *S. aureus* found that 25 of these cases were caused by CA-MRSA.[47] In a recent meta-analysis of ten populations, the CA-MRSA carriage rate was 1.3%, although with considerable variability between populations.[45] In Sydney, Australia, the carriage rate of CA-MRSA was 21%[48] and there have been reports of indigenous people in 'closed populations' with carriage rates of up to 40%.[45] The epidemiology of CA-MRSA is highly variable. While some centers have yet to see a case of invasive disease in children caused by this organism, there are anecdotal reports from other places that the majority of community-acquired invasive *S. aureus* disease in children is now caused by CA-MRSA (McCracken G, personal communication).

Tuberculous osteomyelitis is not common in more developed countries but remains a major cause of skeletal infections in many less developed countries.[49-51] This is exacerbated by widespread infection with HIV[51] and also deterioration in tuberculosis control programs.[50] *Mycobacterium tuberculosis* most commonly affects the spine (50%) and synovium.[49] However, it also affects bones outside the axial skeleton. Recently, there have been reports that unifocal tuberculous bone lesions without a primary focus are becoming more common in children, whereas 50 years ago most tuberculous bone lesions were more commonly multifocal and secondary to a primary lung focus.[50,51] Clinically, children with tuberculous osteomyelitis usually present late with bone pain and swelling with radiologic osteolytic changes in the metaphyses of

long bones. Osteomyelitis rarely occurs as a result of the Bacille Calmette-Guerin vaccine.[52]

Fungi are also rare but important causes of osteomyelitis, most commonly occurring in immunocompromised patients and neonates.[53] *Candida* spp. may cause osteomyelitis in premature neonates and in intravenous drug users. *Aspergillus* spp. may cause osteomyelitis after spread from pulmonary infection, particularly in children with T-cell and neutrophil defects. Immunocompromised children are at risk of infection from fungi and a variety of less common organisms including mycobacteria and Gram-negative organisms.

5. Diagnosis

5.1 Clinical Presentation

The typical child with AHOM presents with fever and limb pain that has lasted for approximately 3 days.[54] Table I summarizes the presenting signs and symptoms of AHOM in children. During the bacteremic phase of AHOM the child may be asymptomatic or unwell with chills and malaise. When bacteria seed the bone, the child subsequently develops acute onset of pain that may be poorly localized initially.[55] Most children present at this point with fever and tenderness. Although younger children may present with apparently vague symptoms, the precise location of the infection can often be elicited with careful physical examination. Younger children often present with pseudoparalysis. If presentation is delayed or progression of the disease is rapid then a subperiosteal collection may develop causing local erythema, tenderness, and swelling. Clinical signs that last longer than 10 days correlate with the development of bony destruction.[2] In one-third of cases there is a history of mild preceding trauma to the affected area,[26] so such a history should cause the clinician to consider rather than dismiss the diagnosis of AHOM.[2]

Table I. Clinical features of acute hematogenous osteomyelitis in children

Clinical feature	Range	References
Age (median)	4–8.2 years	18,19,21,23,25,27,54,56
Duration of symptoms (median)	3–6.1 days	18,21,23,27,54,56
Presenting symptoms		
Pain	65–100%	29,56
Pseudoparalysis	52–84%	29,54
Fever	40–65%	19,54
Malaise	12–70%	54,56
Clinical signs		
Fever	85–93%	23,26,27,29,56
Tenderness	71–84%	25,26,54
Swelling	54–78%	25,26,29,54,56
Decreased range of motion	22–87%	25,26,54,56
Erythema	16–82%	25,26,29,54,56
Heat	27–68%	25,26,29,54
Wound drainage	5–24%	25,26

AHOM is most commonly found in the long bones of the legs. The femur and the tibia are each affected in about one-third of cases. The next most commonly affected bones are the humerus and calcaneus.[15,18,23,57] Other bones that are infrequently affected, but that cause particular clinical problems, are the pelvis and vertebrae.

The main difficulty in vertebral osteomyelitis is delay in presentation. Vertebral osteomyelitis occurs most commonly in elderly patients.[58] Children with vertebral osteomyelitis are usually older than 8 years.[7] Children present with back pain that is dull and constant. They usually have an initially indolent course over 3–4 months, but may subsequently present acutely with a febrile illness. Examination reveals localized exquisite tenderness. A plain radiograph may be normal or show localized radiolucency followed by bone destruction and then sclerosis and osteophyte formation. MRI is the imaging modality of choice in this disease; MRI can detect subtle anterior changes early when scintigraphy may be normal and it can delineate spinal abscesses that may require urgent drainage.[59]

The difficulty with pelvic osteomyelitis is not in delay of presentation but rather delay in making the diagnosis. In one study of 82 patients, only 12 were admitted with the correct diagnosis.[60] Patients present with fever, limp, and pain localized to the hip, buttock, and groin – all symptoms suggestive of hip-joint septic arthritis, which is more common than pelvic osteomyelitis. Clinical examination reveals pain with hip movement but the range of movement is usually complete, which is a useful feature to differentiate from hip-joint septic arthritis. Springing the pelvis may elicit pain and there may be focal areas of tenderness. A plain radiograph is usually unhelpful and scintigraphy is the investigation of choice, followed by gallium scan or MRI if the diagnosis is still unclear.[61]

In the neonate the presentation may be far more subtle with very few signs of infection except for local swelling or reduced motion of the affected limb; the neonate may be otherwise feeding well and appear systemically well.[44] In neonates around 50% of cases involve multiple bones, whereas in children involvement of multiple sites is unusual at around 10%.[14] In addition, neonates often have concurrent septic arthritis and AHOM. This is probably due to delayed presentation in the neonate, along with the anatomical and immune deficits described above.

5.2 Differential Diagnosis

One of the major differential diagnoses is septic arthritis. Many children with AHOM develop muscle spasm and refuse to move the adjacent joint, so it is often difficult to distinguish AHOM from

septic arthritis.[55] The two diseases often coexist in children; in one study 16% of children with septic arthritis had osteomyelitis in the adjacent bone and of these children more than 50% had sequelae of their disease.[16] Careful examination is important to distinguish the focal bone tenderness of AHOM from the marked limitation of joint movement characteristic of septic arthritis,[55] but this distinction is frequently difficult especially when AHOM occurs close to a joint. Table II lists a number of risk factors that may be useful in detecting cases of septic arthritis coexisting with AHOM. In particular, a delayed response of signs and symptoms, or of inflammatory markers, to therapy frequently indicates a complication such as the presence of septic arthritis. One study found that patients admitted with AHOM who have a CRP on day 3 that is at least 1.5 times higher than on the day of admission have a 6.5 times increased risk of septic arthritis compared with those whose CRP decreased or increased by a lesser proportion.[62]

Malignancy is the most important differential diagnosis to exclude. As bone pain can be a presenting complaint of leukemia, a full blood count and blood film is important. All patients with bone pain should have a plain radiograph performed as part of their work-up. If there is extensive bony destruction or other radiologic appearances not typical for AHOM, a biopsy is mandatory to exclude a primary bone tumor such as Ewing sarcoma or osteosarcoma.[63] The absence of fever and/or raised inflammatory markers should also raise this possibility. Children in whom the clinical response, particularly resolution of pain, is slow or remains incomplete after 1–2 weeks of therapy should also have repeat radiography performed, as this may also indicate malignancy.

Cellulitis may mimic the focal tenderness and erythema of AHOM. It can be differentiated with three-phase scintigraphy[64] or ultrasound.[65]

Differentiating bone infarction from AHOM in patients with sickle cell disease can be difficult. Patients who have pain in a single site and who do not have a history of bone infarcts should be suspected of having AHOM.[14] Laboratory tests are not useful, nor is scintigraphy.[66] Ultrasound may be helpful in identifying subperiosteal fluid that can be aspirated for definitive testing.[67]

Chronic recurrent multifocal osteomyelitis (CRMO) is a rare differential diagnosis but important to recognize so as to avoid unnecessary investigations and treatment and enable appropriate discussion of outcome.[68] CRMO is a noninfectious inflammatory syndrome of unknown pathogenesis. It is a diagnosis of exclusion. CRMO affects children and young adults and, unlike AHOM, occurs twice as often in girls than boys.[69] Clinically, the syndrome presents with multifocal disease with prolonged symptoms of pain and swelling that relapse and recur. Occasionally a child presents with only a single site of involvement, which can confuse the diagnosis. Radiographic changes are nonspecific with radiolucency or sclerosis in multiple sites in long bones. Some patients develop dermatologic signs including pustulosis palmoplantaris and psoriasis vulgaris.[70] Treatment with antibacterials does not alter the course of the disease but corticosteroids and anti-inflammatory medication may provide symptomatic relief. More recently, azithromycin has been reported to accelerate symptomatic and radiographic improvement.[71] CRMO usually has a benign outcome, although it may relapse and recur over a prolonged period (up to 15 years) and there is a danger of premature epiphyseal closure.[68,72] Other diagnoses for multifocal bone lesions include multifocal staphylococcal AHOM, leukemia, neuroblastoma, and histiocytosis.

Table II. Risk factors for concurrent septic arthritis with acute hematogenous osteomyelitis

Osteomyelitis in a bone with an intra-articular metaphysis (proximal femur, proximal humerus, proximal radius, distal lateral fibula)
Slow clinical response to therapy
Slow response of inflammatory markers (e.g. C-reactive protein) to therapy
Age <18 months
Delayed presentation
Prior antibacterial therapy

5.3 Confirming the Diagnosis

Diagnosis depends upon the presence of two of the following.

- Clinical signs (fever, localized tenderness, erythema, edema).
- Pus aspirated from bone.
- Positive blood or bone culture.
- Radiographic, scintigraphic, or MRI evidence of osteomyelitis.[6,21]

5.4 Laboratory Investigations

Culture of bone aspirate or bone biopsy is the definitive laboratory test for AHOM. In some patients who have already received antibacterials these cultures may be sterile, but a Gram-stain may still indicate the presence of bacteria (usually Gram-positive cocci). In some culture and Gram-stain negative cases, histology of a bone biopsy may also indicate the typical inflammatory changes of osteomyelitis.

The peripheral white cell count is not a very reliable indicator of AHOM – in some series it is normal more often than it is elevated.[26,54,55,73] However, white cell count and blood film examination should be performed as leukemia is a differential diagnosis of AHOM. Erythrocyte sedimentation rate (ESR) and CRP are elevated at presentation in >90% of cases of AHOM.[26,73-75] While ESR tends to rise within 24 hours of the onset of the clinical features of AHOM and return to normal slowly over 3–4 weeks, CRP rises within 6 hours and normalizes by 2 weeks.[73] All

patients with suspected AHOM should have blood cultures taken before antibacterials are commenced.

5.5 Plain Radiographs

All patients with suspected AHOM should have plain radiographs as part of the diagnostic work-up of a child with bone pain. This can exclude a fracture (particularly in nonaccidental injury) or malignancy. There may be no, or very few, abnormal findings on plain radiographs in the first 10–21 days of AHOM.[55] There are no changes in the first 3 days, but from day 3 there may be evidence of deep soft tissue swelling surrounding the site of infection, and this may be followed by poor distinction of muscular planes from days 3–7.[59] These soft tissue changes are nonspecific. The changes typical of osteomyelitis do not appear until days 10–21 when there may be periosteal new bone formation (periosteal elevation) or lytic lesions; 50% of the bone matrix must be eroded before a lytic lesion can be seen.[26,59] Figure 1 shows the progression of AHOM with abscess formation on plain radiography in a 3-year-old girl.

5.6 Scintigraphy

Scintigraphy has been used in the diagnosis of AHOM since 1971.[76] Today, most centers use technetium-99m labeled phosphates or phosphonates such as methylene diphosphonate (^{99m}Tc-MDP). These compounds covalently bind to hydroxyapatite crystal as they flow through bone. Uptake is increased with increased blood flow, inflammation, and altered osteoblastic activity.[7]

Reports of the sensitivity of this modality in the diagnosis of AHOM range from 60% to 95%,[77,78] but in recent times the sensitivity appears to be more than 90% with newer machines that enable better resolution, more experienced nuclear medicine radiologists, and the recognition that 'cold' scans may indicate AHOM.[79] More than 90% of positive bone scans are 'hot', with increased uptake of ^{99m}Tc-MDP caused by increased osteoblastic activity and hyperemia of bone and soft tissues.[64,80] The less common 'cold' or photopenic scan (reduced update of ^{99m}Tc-MDP) is believed to be caused by focal ischemia as a result of the compression of the bone microcirculation caused by pus in the presence of an abscess.[80] Children with AHOM and cold scans are important to recognize. They usually have more advanced or aggressive disease that requires intensive medical and surgical management, and often have a poor outcome.

False-negative scintigraphy in AHOM appears to be caused by the focal ischemia described above masking the osteoblastic activity and hyperemia characteristic of a hot scan, or because the hyperemia in surrounding soft tissues may mask the ischemic defect of a cold scan (figure 2).[81,82] These tend to occur in the first few days of AHOM. Therefore, a negative bone scan does not exclude AHOM and if there is a strong clinical suspicion then further investigation should be pursued such as bone aspiration, MRI, or sometimes a repeated bone scan.

Although scintigraphy is highly sensitive, the specificity ranges between 70% and 95%.[14] This relatively high false-positive rate is caused by the difficulty in differentiating surrounding infection in soft tissue or joints from AHOM. Specificity has improved over

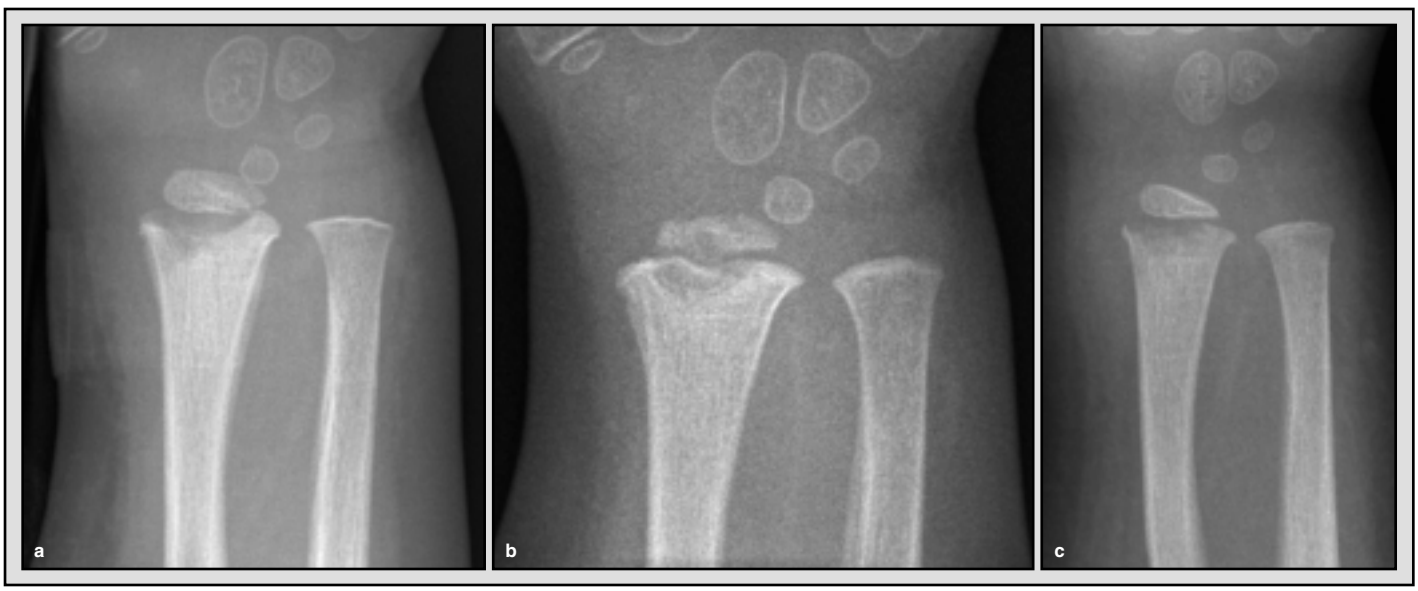

Fig. 1. Acute hematogenous osteomyelitis in a 3-year-old girl who presented with pseudoparalysis. Radiographs at presentation (not shown) were normal. Successive plain radiographs show progressive destruction in the distal radius. (**a**) Two weeks after presentation: erosion of the distal radial metaphysis with loss of fat plane definition. (**b**) Three weeks after presentation: new bone formation with periosteal reaction. Soft tissue changes less prominent than previous radiograph. (**c**) Eight weeks after presentation: re-ossification of the distal metaphysis and resolution of soft tissue abnormality.

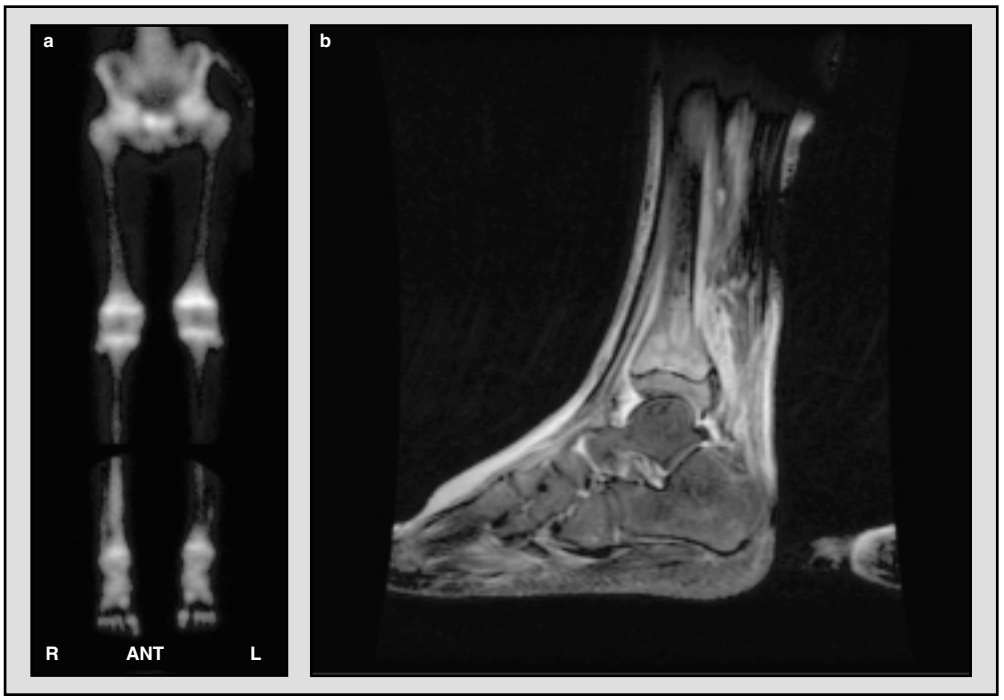

Fig. 2. A 13-year-old boy with multifocal acute hematogenous osteomyelitis who presented with poorly localized lower limb symptoms. His bone scan on presentation was 'cold' in both distal tibias. (**a**) Repeat bone scan 1 week after presentation shows hot areas in the right distal tibia and left distal femur. (**b**) T2-weighted magnetic resonance imaging with fat suppression at the same time shows edema of the distal metaphyseal and epiphyseal regions of the right tibia, loss of bone integrity in the posterior metaphysis, and significant surrounding soft tissue edema. **ANT** = anterior; **L** = left; **R** = right.

time with the development of multiphase (two or three phase) scans. In AHOM there will be increased uptake in the two early phases (angiographic and blood pool) followed by further focal increased uptake in bone in the third (delayed or bone) image, while in cellulitis or soft tissue infection there will be increased uptake in the first two phases but reduced uptake in the third image.[59,83]

The advantages of scintigraphy are that it is positive early (generally within 48 hours of onset of symptoms), results are available quickly, it has high sensitivity, is relatively cheap, rarely requires sedation, and can visualize the entire skeleton, which is particularly useful in smaller children who may have multifocal disease. The disadvantages are that it has low sensitivity in neonates (<30%),[7] low sensitivity and specificity in the pelvis and vertebrae,[14] and a relatively high radiation dose (nuclear bone imaging is equivalent to 100 chest radiographs, or half that of a CT scan of the chest).[84] In addition, it does not provide any detailed anatomical information particularly relating to collections of pus.[55]

5.7 Other Radionuclide Imaging

Two other modalities of radionuclide imaging are used rarely in AHOM. The gallium-67 scan may be useful in pelvic osteomyelitis because of the difficulties in interpreting technetium scans of the pelvis.[14] Gallium-67 is similar to iron in that it binds to plasma proteins such as transferrin and lactoferrin. It is therefore deposited in areas of inflammation because of leaky capillaries and uptake by white cells and bacteria. It may be useful in patients in whom the technetium scan is negative because of its high sensitivity.[59] Tagged white blood cell imaging (labeled with either technetium-99m or indium-111) plays a similarly limited role. Both of these tests deliver high radiation doses that are about three times that of a bone scan.[84] In addition, white cell scanning is also rarely used in pediatrics because of the need to take 20–40mL of blood from the patient.

5.8 Ultrasonography

Ultrasound is particularly useful in detecting subperiosteal fluid collections, and guiding their aspiration. One report suggested that aspiration of subperiosteal fluid is indicated when the diameter of the fluid collection is ≥2mm,[85] while another study found that collections of 3mm resolved with antibacterial treatment alone, provided the child was well.[65] The other changes seen on ultrasound indicative of AHOM are cortical breaches and soft tissue swelling. Ultrasound may also detect fluid collections in adjacent joints suggestive, but not diagnostic, of septic arthritis.

5.9 Magnetic Resonance Imaging

MRI has become the best test for osteomyelitis in cases where symptoms and signs are localized (figure 3). However, availability, cost, and the need for anesthesia may limit its application in children under 7 years of age. In cases where the clinical features do not enable localization of disease whole body scintigraphy is preferred. MRI changes in AHOM are characterized by dark bone marrow intensity on T1-weighted images, a finding that has almost 100% sensitivity.[86] MRI does not have as high specificity because it is poor at differentiating infected from noninfected foci, although the use of fat-suppressed contrast-enhanced imaging has improved specificity.[87] The real advantage of MRI is in providing detailed anatomical information. For this reason it is good for delineating abscesses and sinus tracts and is particularly useful in planning surgery in complex cases. It also has a particular role in vertebral osteomyelitis because of the risk of an epidural abscess, and in the pelvis where there is a higher risk of abscess formation.[88] It may also have a role in cases where there is a high clinical suspicion of localized AHOM but a negative bone scan.[89]

5.10 A Suggested Approach to Diagnosis – is Bone Aspiration Required?

Blood cultures are positive in 30–50% of patients, while bone aspiration and bone biopsy culture rates are higher at 50–70% of patients.[15,18,56] Many experts strongly recommend the routine use of bone aspiration at admission.[90] However, this is becoming more controversial given the high sensitivity of radiologic techniques to diagnose AHOM, the very high likelihood of staphylococcal etiology, and the response to a β-lactamase-resistant penicillin. Aspiration of bone is a painful procedure and has the potential to damage the epiphyseal plate.[6] We advocate obtaining a diagnostic specimen in any of the following situations.

- Delayed presentation.
- A child with any predisposing condition (e.g. immunocompromised children, patients with sickle cell disease, and other hemoglobinopathies).
- Unusual radiographic findings (e.g. lucency on plain radiography at presentation).
- Regions where there is a high likelihood of CA-MRSA (e.g. where more than 5–10% of invasive *S. aureus* cases are due to CA-MRSA).
- Reason to suspect a complication such as an abscess.
- Reason to suspect an alternative diagnosis such as malignancy.
- Delayed response to antibacterials.

However, the majority of children with typical AHOM do not require bone aspiration or biopsy. Figure 4 shows a suggested approach to the diagnosis of AHOM.

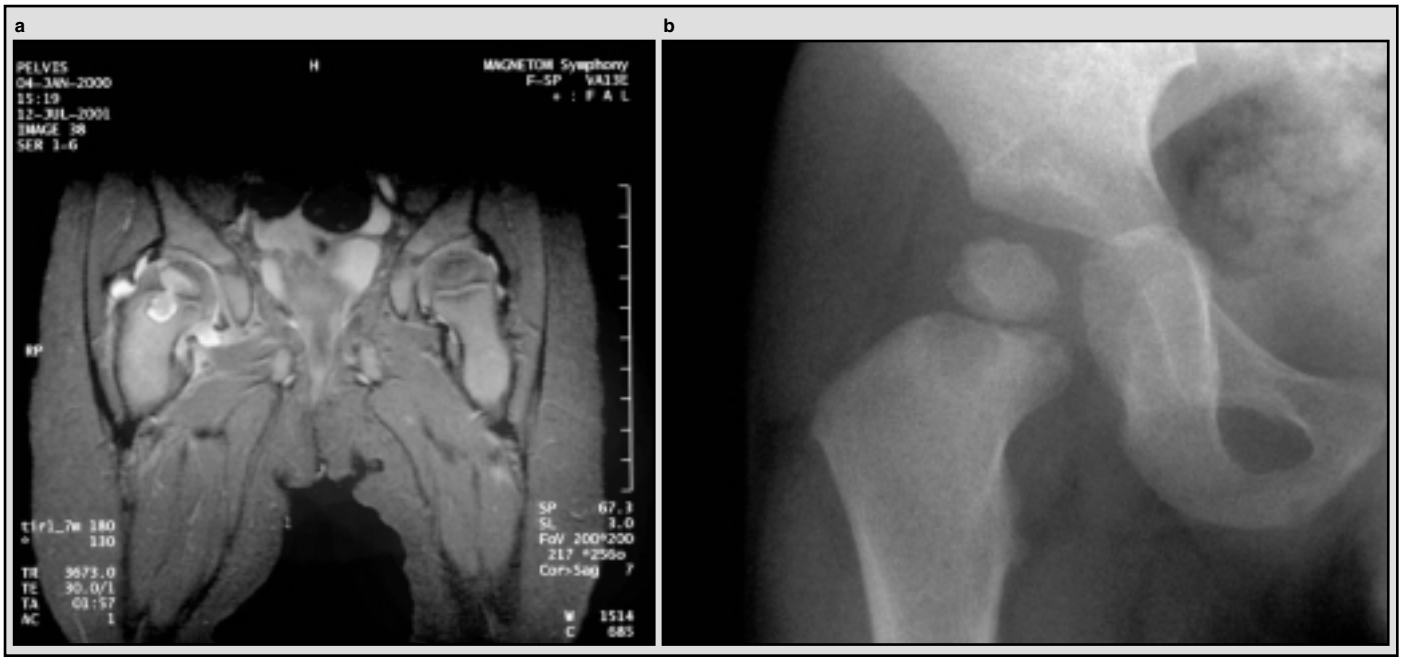

Fig. 3. An 18-month-old child who presented with fever and limp. (**a**) T2-weighted magnetic resonance imaging with fat suppression shows a focal area of signal abnormality in the proximal femoral metaphysis consistent with a Brodie abscess. There is extension through the physeal plate in the epiphysis. (**b**) Plain radiograph shows a destructive lesion in the femoral metaphysis.

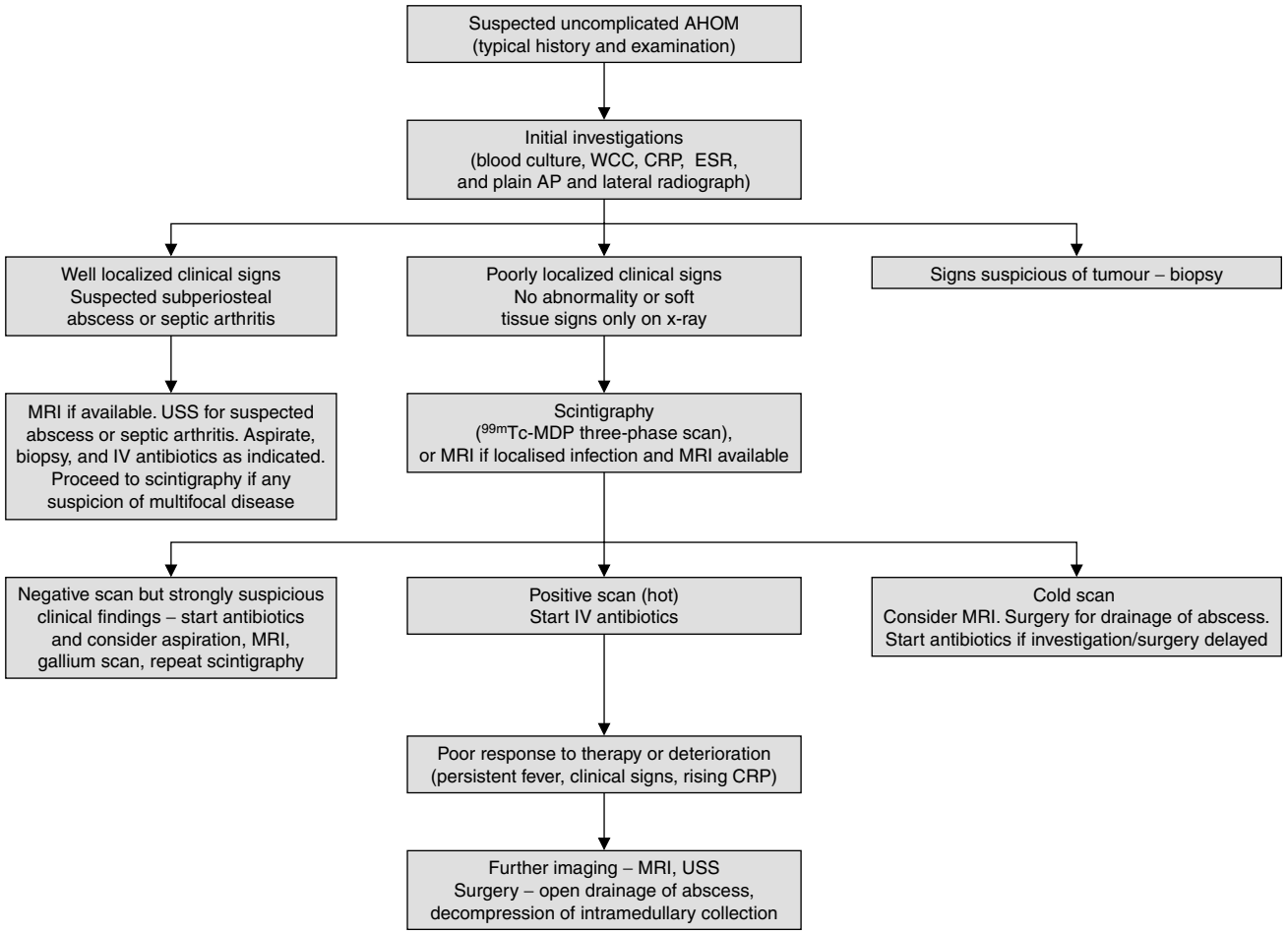

Fig. 4. An approach to the management of acute hematogenous osteomyelitis (AHOM) in children. Note this figure does not apply to neonates who are less likely to have positive bone scans and may be infected with a variety of organisms. ^{99m}**Tc-MDP** = technetium-99m methylene diphosphonate; **AP** = anteroposterior; **CRP** = C-reactive protein; **ESR** = erythrocyte sedimentation rate; **IV** = intravenous; **MRI** = magnetic resonance imaging; **USS** = ultrasound scan; **WCC** = white cell count.

6. Antimicrobial Therapy

6.1 Antibacterial Choice

Antibacterial choice is initially empirically based on the age of the child and the likely pathogens in that age group (see table III). Special consideration and the use of broad-spectrum antibacterials to cover Gram-negative organisms and unusual organisms should be given to special groups such as neonates or patients who are immunocompromised, have sickle cell disease, puncture wounds to the feet, or in areas with no or low Hib vaccine uptake, or have high CA-MRSA prevalence. Following identification of the organism, antibacterial choice is dictated by susceptibility testing. If cultures are unable to be taken or if cultures are negative then the initial empirical choice should be continued, provided the clinical response is adequate.[8]

A single β-lactamase-resistant penicillin such as flucloxacillin, oxacillin, dicloxacillin, or nafcillin is effective against methicillin-susceptible *S. aureus* and most streptococci.[7] Early studies showed the effectiveness of β-lactamase-resistant penicillins.[30,63,91] A first-generation cephalosporin (e.g. cephalothin or cephazolin) or clindamycin can be used in penicillin-allergic patients. Early studies showed that clindamycin achieves excellent serum and tissue concentrations in children and is a useful alternative when children are allergic to penicillin.[92] Some groups have used it as a first-line therapy,[27,93] although the cost and the rare but potentially serious adverse effect of pseudomembranous colitis lead most clinicians to use it as a second-line treatment.

The addition of ampicillin or a third-generation cephalosporin is no longer necessary in areas where the conjugate Hib vaccine is in use.[21] Third-generation cephalosporins alone are usually not considered sufficient because of incomplete coverage against *S. aureus*, although one study found that cefotaxime in combination with surgical treatment had a 5% clinical failure rate in osteomyelitis in children.[94] The second-generation cephalosporin

Table III. Initial empirical antibacterial treatment for acute hematogenous osteomyelitis in children

Patient	Likely pathogens	Antibacterial choice
Age ≥5 years	*Staphylococcus aureus*	BLRP[a]
Age <5 years	*S. aureus*	BLRP[a]
	Haemophilus influenzae type b (Hib)	If risk of Hib:[b] add 3GC or use single-agent cefuroxime
Neonate	*S. aureus*	BLRP[a] + gentamicin
	Group B streptococci	or
	Gram-negative coliforms	BLRP[a] + 3GC
Patient with sickle cell anemia	*S. aureus*	BLRP[a] + 3GC
	Salmonella species	
Puncture wounds to the feet	*Pseudomonas aeruginosa*	BLRP[a] + APA ± gentamicin
	S. aureus	
Immunocompromised	Multiple organisms including *S. aureus*, *P. aeruginosa*, Gram-negative organisms, fungi	BLRP[a] + APA + gentamicin Add antifungal (e.g. amphotericin B) if high suspicion of fungus or no response

a If there is a history of allergy to penicillins then consider first-generation cephalosporin (e.g. cephazolin or cephalothin) or clindamycin. In areas of CA-MRSA consider clindamycin or adding gentamicin. Vancomycin only necessary if considering non-CA-MRSA (e.g. nosocomial infection).

b Risk of Hib refers to areas with little or no uptake of Hib vaccine, or in individual patients who are not immunized or have had inadequate immunization.

3GC = third-generation cephalosporin (e.g. ceftriaxone, cefotaxime); **APA** = anti-pseudomonal antibacterials (e.g. ceftazidime, piperacillin, ticarcillin); **BLRP** = β-lactamase-resistant penicillin (e.g. oxacillin, dicloxacillin, flucloxacillin, nafcillin); **CA-MRSA** = community-acquired methicillin-resistant *S. aureus*.

cefuroxime is also effective against Hib and can be used as a single agent.[14]

The initial antibacterial choice in cases where CA-MRSA is suspected is less clear. Depending on the local susceptibility patterns the options are clindamycin as single therapy, adding gentamicin to the β-lactamase penicillin, or using vancomycin.[47,95] However, there are almost always alternatives to vancomycin if CA-MRSA is suspected, so this antibacterial is not recommended because of the risk of emergence of resistant organisms such as vancomycin-resistant enterococci and vancomycin (glycopeptide)-nonsusceptible *S. aureus*.[95,96]

6.2 Parenteral-Oral Sequential Therapy

Physicians treating adults are accustomed to managing AHOM with prolonged intravenous therapy (usually 6 weeks).[10] However, children can usually be treated for shorter courses, and with parenteral-oral sequential therapy. The efficacy and safety of sequential therapy has been proven over the last 20 years in numerous studies, some investigating the serum and bone concentrations of oral antibacterials[57,91,92,97] and others investigating the clinical outcome of sequential therapy.[18,25,28,54,56,63,91,98-102] The advantages of switching to oral therapy include a reduction in patient discomfort with removal of the intravenous line and earlier discharge, a reduction in the risk of thrombophlebitis and nosocomial infections, and a reduction in cost.[56,103]

It is recommended that oral antibacterials be used at two to three times higher doses than normally given to achieve adequate serum and bone concentrations.[104] Children have fewer gastrointestinal adverse effects at these doses.[105] If there are gastrointestinal adverse effects then the dose can be reduced and probenecid can be added.[106]

Because of the dangers of treatment failure, patients commencing sequential therapy have to be chosen carefully. There are a number of circumstances under which sequential therapy should either not be considered, or the switch to oral therapy should only be considered after a prolonged course of parenteral antibacterials (table IV).

The total duration of therapy and the timing of switching to oral therapy are controversial. Traditionally, parenteral treatment lasted for 4–6 weeks.[7,26,56,63] In recent years, there has been a move to delivering intravenous antibacterials for only 3–7 days, and continuing with oral antibacterials for a further 3 weeks. This has never been tested in a randomized controlled trial. Studies vary greatly in the duration of intravenous delivery, from 3 days[100] to 8 days[28] to 4 weeks.[23] In Finland, 50 patients with staphylococcal AHOM were treated with an average of 4 days of intravenous antibacterials (clindamycin or cefradine) followed by an average of 4 weeks of oral antibacterials with no treatment failures after 2 years of follow-up.[27] A study from Australia reported complete recovery in 50 patients treated with <4 days of intravenous therapy and 3 weeks of oral therapy (flucloxacillin or phenoxymethylpeni-

cillin).[100] These data were supported by a larger review of 71 children with AHOM and/or septic arthritis at the same hospital in 1997, showing that children who received short-course treatment (total duration <3 weeks) had the same low complication rate as those who received longer treatment.[22] Most authors agree that the decision to start oral antibacterials should be considered on an individual patient basis with careful evaluation of clinical and laboratory signs of improvement.[107] The Finnish and Australian data support the practice of switching to oral therapy earlier and shortening the total duration of therapy. In our center, standard treatment is 3 days of intravenous antibacterials followed by 3 weeks of oral treatment, but this regimen is restricted to otherwise healthy children with classical AHOM presentations, no evidence of chronicity on initial radiography, and rapid response to treatment. Children with atypical presentations, underlying illness, evidence of chronicity, complications, or delayed response to treatment are all treated with longer initial courses of intravenous antibacterials and longer total durations of therapy.

6.3 Monitoring Therapy and Follow-Up

Clinical assessment still remains the most important tool in evaluating response to treatment, but can be augmented with laboratory investigations. A number of studies have evaluated the role of inflammatory markers such as white cell count, ESR, and CRP in monitoring response to treatment. CRP better reflects the response to therapy than ESR and is a better predictor of outcome. In one study, persistently high CRP values in the first week predicted extensive radiographic changes while no patient with a CRP value <55 mg/L at the end of the first week had radiographic changes or symptoms at follow-up.[74] In some previous reports therapy has not been ceased until there is normalization of the ESR.[28] Recent studies show that this is unnecessary.[27,73-75,107] However, it is not clear if CRP normalization could allow cessation of therapy. A rising CRP after antibacterials have been started is a useful indicator of complications or the presence of septic arthritis. The combination of CRP monitoring and clinical assessment is ideal – in one study high CRP values and slow clinical response together strongly predicted poor outcome.[75]

Table IV. Reasons not to use parenteral-oral sequential therapy or to prolong the initial course of parenteral treatment in acute hematogenous osteomyelitis

Age <3 months
Immunocompromised
Delayed presentation
Impedance to oral antibacterial absorption (e.g. diarrhea or vomiting)
Deterioration or failure to improve on parenteral antibacterials
remaining febrile
no improvement in mobility, pain, tenderness, or erythema
rising or delayed reduction in C-reactive protein
Surgical procedures planned but not yet performed
Close follow-up not possible, or reason to suspect poor adherence to therapy

Gastrointestinal absorption of oral antibacterials is variable between individual children. AHOM in children can potentially cause serious sequelae such as limb shortening and so it is essential to achieve adequate levels of antibacterials in the bone. For this reason many experts recommend the routine measuring of the concentration of the antibacterial in serum or measuring the serum bactericidal titer (SBT) to confirm adequate gastrointestinal absorption.[8,107-109] The SBT has proven to be helpful in cases of treatment failure;[110] however, in the Finnish study described in section 6.2, none of the 50 patients in the series had a poor outcome and none had an SBT measured. In many countries measurement of drug levels or SBT is difficult.

Close monitoring of clinical progress and laboratory indices of inflammation in the first few days of intravenous therapy are crucial. If the patient fails to show some improvement clinically by 48–72 hours after commencing therapy (persistent fever, persistent symptoms and signs), if the CRP does not fall, or if the patient deteriorates, then further investigation is required. This may include re-imaging with MRI or ultrasound. If a collection is found then surgical drainage is required. If there is no collection, aspiration is necessary for histologic and microbiologic specimens. However, most patients will respond quickly to intravenous antibacterials and can be changed to oral antibacterials after 3–7 days.[22,27,63,100,107] Once compliance with oral medication is assured, the patient can be managed as an outpatient with at least a weekly review that includes CRP measurement for 3 weeks. We suggest an ongoing 3–6 monthly clinical review for 2 years to monitor for complications such as relapse.

7. Surgical Management

Some earlier studies recommended that all but the mildest cases of AHOM routinely required surgical intervention.[111] In recent times, the success of antibacterial treatment has meant that there is a reducing role for surgical intervention in the acute illness. The main place for surgical management in AHOM is when the disease is complicated by abscess formation, or for confirmation of the diagnosis. Surgery becomes more important when complications occur, such as the development of chronic osteomyelitis, sequestra, pseudarthroses, or growth defects.[13] In chronic osteomyelitis, effective treatment requires both long-term antibacterials and surgical debridement.[70] Newer limb reconstruction techniques have improved results in correcting angular deformity and limb shortening. However, destruction to articular damage causes life-long problems that are not correctable by surgery.

8. Prognosis

Mortality is exceedingly rare from AHOM, <1% in most centers in affluent countries. The complications of AHOM are also rare, but may cause life-long disability. Complication rates vary from 0% to 13%.[14,18,19,23,25-28,54,56,74] The most common are recurrent infection (which may occur many months or even years later) and chronic osteomyelitis. Other complications include pathologic fractures, bone deformities including growth arrest and leg-length discrepancy, and joint destruction.

9. Summary

In children who are otherwise healthy and develop features of typical long bone AHOM, *S. aureus* is the most common pathogen. In these children diagnosis can usually be made on the basis of clinical and radiologic findings alone. Provided there is a rapid response to intravenous treatment with a β-lactamase-resistant penicillin, we recommend intravenous treatment for 3 days followed by sequential oral therapy for 3 weeks with careful monitoring. Any suggestion of an atypical presentation or poor response to therapy mandates further investigation, potentially surgical intervention, and a longer duration of therapy (both intravenous and subsequent oral courses). This approach leads to good outcomes in almost all children with AHOM.

Further studies to determine the reasons for poor outcomes in a small number of children may provide insights into alternative therapeutic strategies for this group. Randomized controlled trials of short compared to long-term antibacterial therapy are unlikely to be conducted in children because of the high baseline cure rates (and therefore large sample size requirements), so better data documenting outcomes of short-term therapy will require prospective register-based studies.

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