

## Review

# Bone infection

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**SUMMARY** Osteomyelitis, or bone infection, affects all age groups and develops from various sources including haematogenously from distant infection foci, from external sources such as post-operative or post-traumatic wound infections and from adjoining soft tissue infections. *Staphylococcus aureus*, *Streptococcus pyogenes* and *Haemophilus influenzae* are the most common pathogens of haematogenous osteomyelitis. Aerobic and facultative gram-negative bacteria have emerged as significant pathogens in some types of osteomyelitis while anaerobic bacteria are increasingly recognized as potential pathogens in non-haematogenous osteomyelitis. The emergence of antibiotic resistance is of increasing concern, although improvements in radiologic imaging, antibiotic treatment and heightened awareness have led to earlier detection such that long-term sequelae and morbidity are now primarily due to delays in diagnosis and inadequate treatment.

## Introduction

Acute osteomyelitis is the clinical term for a new infection in bone. This infection occurs predominantly in children and is often seeded haematogenously. In adults, osteomyelitis is usually a subacute or chronic infection that develops secondary to an open injury to bone and surrounding soft tissue [1]. Subacute haematogenous osteomyelitis in children develops as a result of increased host resistance and decreased bacterial virulence [2]. Chronic recurrent, unifocal or multifocal osteomyelitis (CRMO), is a rare disease of children with an aseptic inflammatory disorder of unknown origin, involving different osseous sites especially the long bones and clavicles. Bacterial cultures of affected tissue report negative in nearly all cases. CRMO has been associated with a number of autoimmune diseases including Wegener's granulomatosis, psoriasis and inflammatory bowel disease [3,4].

This review presents clinicians with current literature regarding pathophysiology,

incidence, etiology, diagnosis and treatment of osteomyelitis.

## Pathophysiology

Haematogenous suppurative osteomyelitis occurs most commonly in infants and young children, but in certain cases malnutrition and child labour may lead to involvement of older children and adults [5]. The metaphysis of long bones, particularly the femur, tibia and humerus are the usual sites of involvement. There are a number of pathways by which bacteria reach a bone including: via the haematogenous route from a distant focus of infection; spreading from a source external to the bone such as post-operative or post-traumatic wound infection; and by extension from an adjoining soft tissue infection [6-8].

In childhood haematogenous osteomyelitis, the initial lesion is an area of acute exudative inflammation involving the narrow spaces of the metaphysis. The inflammatory changes quickly spread through the

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cancellous bone to reach the periosteum as a subperiosteal abscess forms. An abscess originating at one end of a long bone may extend along the narrow cavity to reach the other end; this usually results in necrosis of the entire shaft [9]. Exudates from a metaphyseal focus is forced through the canals in the thin metaphyseal cortex to the periosteum and elevates it, disrupting the periosteal vessels that supply the cortical bone. Deprived of this blood supply, the outer half of the cortical bone dies, forming large sequestra. These sequestra are eventually separated from living bone and are surrounded by pus. While some, or all, of the original shaft is undergoing separation as a sequestrum, the periosteum forms a shell of new bone, or involucrum, around the old shaft [6,10]. As the involucrum forms, it further occludes circulation to the sequestrum [11]. Sinuses, or cloacae, often communicate between the central abscess and the overlying soft tissue, or even the skin surface. Cases have been reported in which after many years a squamous carcinoma has originated in such a sinus [10]. Some cases become chronic and persist for years with draining sinuses. The complication of secondary amyloidosis, involving particularly the liver, spleen and kidneys, may occur in such cases [6,10].

A localized subacute or chronic pyogenic osteomyelitis, which arises insidiously and is usually situated in the metaphysis of a long bone, especially the upper end of the tibia, is called a Brodie abscess. The central cavity contains pus, which may be sterile, is lined by granulation tissue and is surrounded by reactive bone sclerosis. It may be a sequel of an acute osteomyelitis with an organism of low virulence [7,10].

Haematogenous osteomyelitis in the adult is relatively rare but may complicate injury or debilitating disease. It tends to involve the diaphysis of the bone rather than

the metaphysis or epiphysis. The periosteum in the adult is more fibrous and adheres more firmly to the bone. Accordingly, subperiosteal abscesses are uncommon and large sequestra do not usually form because the cortical blood supply is maintained [6,9,10]. Haematogenous osteomyelitis in the newborn presents a rather different picture from the disease in the older child. It may involve only one bone, often the maxilla, or, in generalized osteomyelitis of the newborn, many bones may be affected. It arises sometimes in association with umbilical or other sepsis. 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 [9,10].

A variation from the usual localization occurs in salmonella osteomyelitis that may develop in persons with sickle cell anaemia. In this condition the infection is usually bilateral and often symmetrical [6]. Tuberculous osteomyelitis is almost always haematogenous, secondary to pulmonary focus, and caused by *Mycobacterium tuberculosis* with localization in the vertebrae or epiphyses of long bones. Bone destruction without sequestra and with minimal new bone formation characterizes the active phase of tuberculous osteomyelitis [6].

In contrast to acute haematogenous osteomyelitis, which is a general disease with organic manifestations, post-traumatic osteomyelitis is a primary local infection that can produce general symptoms of disease, but need not necessarily do so in every case. Following colonization of bacteria in the affected tissue, acute haematogenous osteomyelitis is accompanied by hyperaemia and abundance of cells, while post-traumatic osteomyelitis is characterized by avascularity [12]. In osteomyelitis, bacteria adhere to bone matrix and orthopaedic implants via receptors. They subsequently

elude host defences and antibiotics by 'hiding' intracellularly, by developing a slimy coat, or by acquiring a very low metabolic rate. The presence of an orthopaedic implant also causes a local polymorphonuclear cell defect with decreased ability to kill phagocytosed bacteria [13].

## Incidence

In industrialized countries, acute haematogenous osteomyelitis is uncommon [9,14]. In developing countries, the disease still exists and the morbidity appears worse in lower socioeconomic groups [9]. A seasonal peak is present in late summer and autumn [15]. The disease affects all age groups and has been found to be most common in those aged less than one year [5,16,17]. Other studies have found it to be most frequent in those aged 7 and 9 years [18,19]. In most reports, it has been reported that boys are up to four times more likely than girls to be affected [9,15,17,18,20].

## Etiology

While many types of microorganisms including viruses and fungi may cause osteomyelitis, it is usually bacterial in origin [21]. In studies of osteomyelitis, *Staphylococcus aureus* has been the most common pathogen isolated from patients with haematogenous osteomyelitis, which has been found to be the causative agent in from 43% to 96% of cases [5,9,14,16,17,19,22-24]. *S. aureus* is also the most common cause of osteoarticular infection in HIV-positive patients [25]. Other frequently found organisms are *Streptococcus pyogenes* and *Haemophilus influenzae*. The latter is more common among children under the age of four years [1,5]; however, it has become

rare in immunized children [14]. Rare causative agents are *Streptococcus pneumoniae*, *Neisseria* species and fungi. Aerobic and facultative gram-negative bacteria have emerged as significant pathogens in patients with chronic osteomyelitis, post-operative osteomyelitis, osteomyelitis following injury and osteomyelitis with an adjacent septic focus [8,18,26-28]. Anaerobic bacteria have received increasing recognition as potential pathogens in non-haematogenous osteomyelitis, especially in chronic cases. They have been isolated from 22% to 40% of patients with osteomyelitis [8,18,26,28-30]. *Salmonella* spp., *Mycobacteria* spp. and *Brucella* spp. also infect the bone. In patients with sickle cell anaemia, 80% to 84% were infected with *Salmonella* species [31,32].

## Diagnosis

The diagnosis of osteomyelitis is dependent upon clinical features, radiology, cultures of suitable material, histopathology and other non-specific investigations such as erythrocyte sedimentation rate (ESR), white blood cell (WBC) count and serum C-reactive protein. Improvements in radiologic imaging, most notably magnetic resonance imaging, and a heightened awareness of this condition has led to earlier detection and resulted in marked decreases in morbidity and mortality [14,33]. 99mTc bone scan has been reported to be the most sensitive imaging test [34].

The material that is used for microbiological culture is either taken from the bone directly (operative) or collected from a discharging sinus [35]. Material from surgical wounds in cases of post-operative bone infection could also be used for culture and have been found to be reliable [36]. Although the operative material is more accu-

rate and contains no contaminants, it cannot be obtained unless an operation is performed under general anaesthesia. Therefore, material from a sinus-track or a surgical wound is normally used for culture. Sinus-track specimens have proven to be suitable sources for the isolation of bacteria, provided that material from the depth of the sinus is aspirated by syringe from an actively flowing sinus and inoculated immediately on culture media [35]. *Mycobacteria* species can often be identified from sinus-track cultures for patients for whom operative culture, histopathology and clinical examination have failed to confirm the diagnosis of tuberculosis [37]. Aerobic and anaerobic cultures have to be made for all patients with osteomyelitis, especially in chronic cases, as high incidences of anaerobes have been found in previous studies [8,18,26,28-30,35]. For better isolation of anaerobic bacteria, it is recommended that the specimen be inoculated on pre-reduced (oxygen-free) culture media and cultivated into an anaerobic jar immediately at the bedside [30,35]. Chronic recurrent multifocal osteomyelitis is a recognized clinico-pathologic entity with typical radiographic findings, mostly in the metaphysis of long bones. The diagnosis is one of exclusion without pathognomonic findings [38].

## Treatment

Bone infection is treated with antibiotics either with or without surgical intervention. Antibiotic treatment is one of the major advances of the last century. Before the introduction of antibiotics, one-fourth to one-third of patients died of acute haematogenous osteomyelitis and 50% were seriously crippled for life. Furthermore, a high proportion of patients with chronic osteomyelitis required amputation [20,39]. Now long-term sequelae and morbidity are

primarily due to delays in diagnosis and inadequate treatment [14].

*S. aureus*, the most common causative organism in haematogenous osteomyelitis, was resistant to benzylpenicillin in 14.1% of cases in 1946. By 1970, this had increased to 93% [40]. However, 100% of *S. aureus* that caused all types of osteomyelitis have been found to be susceptible to fusidic acid while 94% were resistant to benzylpenicillin in the early 1990s [41]. The prominence of *Staphylococcus* species as the causative agent in bone and joint infections suggests that fusidic acid has a potentially important role in their treatment [42]. The use of a bactericidal agent rather than a bacteriostatic agent was associated with a significantly smaller rate of failure [43]. The choice of antibiotic must also be guided by the result of culture and sensitivity test.

Antimicrobial therapy is an essential element in the treatment of anaerobic osteomyelitis. Benzylpenicillin appears to be the drug of choice for most anaerobic infections other than *Bacteroides fragilis*. Clindamycin hydrochloride, carbenicillin sodium, chloramphenicol, metronidazole, ticarcillin sodium, piperacillin sodium and mezlocillin sodium have all been shown to be effective against anaerobic organisms, including *B. fragilis* [44,45]. Recently, the following antibiotic classes have been used in the treatment of all categories of osteomyelitis: penicillins, beta-lactamase inhibitors, cephalosporins, vancomycin, rifampin, aminoglycosides, flouroquinolones, trimethoprim-sulfamethoxazole and mitronidazole [16].

For optimal results, antibiotic therapy must be started early by parenteral route and treatment should be continued for at least 4-6 weeks for acute osteomyelitis [1,11]. Evaluating the response to treatment by monitoring C-reactive protein lev-

els decreases the average duration of therapy to 3–4 weeks with few relapses [14]. The emergence of antibiotic resistance, particularly to methicillin sodium and vancomycin hydrochloride by *S. aureus* organism, is of increasing concern [14,47].

Clinical experience indicates that therapy for chronic osteomyelitis caused by either aerobic or anaerobic bacteria should be continued for a minimum of 8 to 12 weeks and combined with surgery [45]. The implantation of gentamicin polymethylacrylate (PMMA) chains or minichains into

infected osteomyelitic cavities is a well-established local antibiotic therapy supplementary to radical debridement [48]. Prolonged courses of multi-drug therapy are required for treatment of mycobacterial bone infection [49].

The treatment of patients with chronic recurrent multifocal osteomyelitis is with non-steroidal anti-inflammatory drugs. Recognition of this condition is important to avoid treatment with antibiotics and repeated operations [38].

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