Osteomyelitis

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Bone and joint infections are painful for patients and frustrating for both them and their doctors. The high success rates of antimicrobial therapy in most infectious diseases have not yet been achieved in bone and joint infections owing to the physiological and anatomical characteristics of bone. The key to successful management is early diagnosis, including bone sampling for microbiological and pathological examination to allow targeted and long-lasting antimicrobial therapy. The various types of osteomyelitis require differing medical and surgical therapeutic strategies. These types include, in order of decreasing frequency: osteomyelitis secondary to a contiguous focus of infection (after trauma, surgery, or insertion of a joint prosthesis); that secondary to vascular insufficiency (in diabetic foot infections); or that of haematogenous origin. Chronic osteomyelitis is associated with avascular necrosis of bone and formation of sequestrum (dead bone), and surgical debridement is necessary for cure in addition to antibiotic therapy. By contrast, acute osteomyelitis can respond to antibiotics alone. Generally, a multidisciplinary approach is required for success, involving expertise in orthopaedic surgery, infectious diseases, and plastic surgery, as well as vascular surgery, particularly for complex cases with soft-tissue loss.

Osteomyelitis is an inflammatory process accompanied by bone destruction and caused by an infecting microorganism.[1–4] The infection can be limited to a single portion of the bone or can involve several regions, such as marrow, cortex, periosteum, and the surrounding soft tissue. From a practical viewpoint, distinction of three types of osteomyelitis is useful.

Osteomyelitis due to local spread from a contiguous contaminated source of infection follows trauma, bone surgery, or joint replacement. It implies an initial infection that gains access to bone. It can occur at any age and can involve any bone. In this group, identification of patients with a foreign-body implant is important, both because of their high susceptibility to infection and because of treatment challenges.

Osteomyelitis secondary to vascular insufficiency occurs predominantly in people with diabetes and in almost all cases follows a foot soft-tissue infection that spreads to bone. This disease entity has several important contributing factors: the metabolic consequences of diabetes; bone and soft-tissue ischaemia; and peripheral motor, sensory, and autonomic neuropathy.

Haematogenous osteomyelitis is seen mostly in prepubertal children and in elderly patients and is characterised by nidation of bacteria within sometimes only slightly injured bone, presumably seeded by bacteria not apparent but present in the blood.

Acute osteomyelitis evolves over several days or weeks, as opposed to chronic osteomyelitis, which is somewhat arbitrarily defined as long-standing infection that evolves over months or even years, characterised by the persistence of microorganisms, low-grade inflammation, and the presence of dead bone (sequestrum) and fistulous tracts (figure 1).[5,6] Relapses in the same area and with accompanying fever are a clear sign of chronic osteomyelitis. Clinical signs persisting for longer than 10 days are associated with the development of necrotic bone and chronic osteomyelitis.[7]

Cierny and Mader developed a detailed classification for orthopaedic surgeons treating patients with chronic osteomyelitis, which applies best to long and large bones and is not very useful for the digits, small bones, or the skull.[2,4,8] It combines both stages of anatomical disease and physiology of the host.

Mechanisms of disease: the bone

Examination of the area of acute osteomyelitis by microscopy reveals an acute suppurative inflammation in which bacteria or other microorganisms are embedded. Various inflammatory factors, and leucocytes themselves, contribute to tissue necrosis and the destruction of bone trabeculae and bone matrix. Vascular channels are compressed and obliterated by the inflammatory process, and the resulting ischaemia also contributes to bone necrosis. Segments of bone devoid of blood supply can become separated to form sequestra and can continue to harbour bacteria despite antibiotic treatment (figure 1). Antibiotics and inflammatory cells cannot reach this avascular area, so medical treatment of osteomyelitis fails. At the infarction edge, there is reactive hyperaemia that is associated with increased

Search strategy and selection criteria

We searched the *The Cochrane Library* and MEDLINE (1966 to 2004) to identify studies on the pathogenesis, microbiology, and treatment of osteomyelitis; many articles were identified through searches of the extensive files of the two authors. The main search term was "osteomyelitis" alone and in combination with "vascular insufficiency", "haematogenous", "vertebral", "biofilm", "imaging", "diabetic foot", "prosthetic infections", "trauma", and "surgery". Papers published in English, French, Spanish, or Italian were reviewed. Selection criteria included a judgment about the novelty and importance of studies and their relevance for the well-informed general clinician. We also searched the reference lists of articles identified by this search strategy. Several review articles or book chapters were included because they provide comprehensive overviews that are beyond the scope of this seminar. The reference list was modified during the peer-review process on the basis of comments from reviewers.

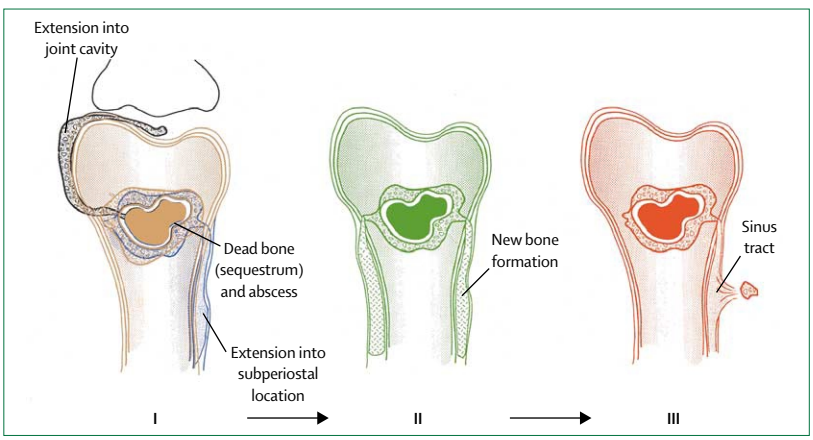

Figure 1: **Steps in the progression of chronic osteomyelitis**
I: From sequestrum, an area of devascularised dead bone, progression of intramedullary infection towards an intracapsular location can lead to septic arthritis; progression of infection towards a subperiosteal location can lead to periosteal elevation. II: New bone formation as a result of massive periosteal elevation. III: Extension of sequestrum and necrotic material through cortical bone creates a fistula and ultimately breaks through the skin (adapted from reference 5 with permission).

osteoclastic activity. This activity, in turn, produces bone loss and localised osteoporosis. Meanwhile, bone apposition occurs, in some cases exuberantly, causing periosteal apposition and new bone formation.

There is much evidence that growth factors, cytokines, hormones, and drugs regulate the proliferation and activity of osteoblasts and osteoclasts. The growth factors and cytokines that stimulate normal osteoclasts and osteoblasts also influence their development and death and show altered local concentrations during infection.[9–11] Although information on the involvement of cytokines on bone growth has been acquired, little is available for osteomyelitis.

Pathogenesis: host and microorganisms

The development of osteomyelitis is related to microbial (table 1) and host factors. Among pathogenic micro-organisms, *Staphylococcus aureus* is by far the most commonly involved (figure 2). This organism elaborates a range of extracellular and cell-associated factors contributing to its virulence. First are factors promoting

Most common clinical association	Microorganism
Frequent microorganism in any type of osteomyelitis	*Staphylococcus aureus* (susceptible or resistant to meticillin)
Foreign-body-associated infection	Coagulase-negative staphylococci or *Propionibacterium* spp
Common in nosocomial infections	*Enterobacteriaceae, Pseudomonas aeruginosa, Candida* spp
Associated with bites, diabetic foot lesions, and decubitus ulcers	Streptococci and/or anaerobic bacteria
Sickle-cell disease	*Salmonella* spp or *Streptococcus pneumoniae*
HIV infection	*Bartonella henselae* or *B quintana*
Human or animal bites	*Pasteurella multocida* or *Eikenella corrodens*
Immunocompromised patients	*Aspergillus* spp, *Candida albicans*, or *Mycobacteria* spp
Populations in which tuberculosis is prevalent	*Mycobacterium tuberculosis*
Populations in which these pathogens are endemic	*Brucella* spp, *Coxiella burnetii*, fungi found in specific geographical areas (coccidiodomycosis, blastomycosis, histoplasmosis)

Table 1: **Microorganisms isolated from patients with osteomyelitis and their clinical associations**

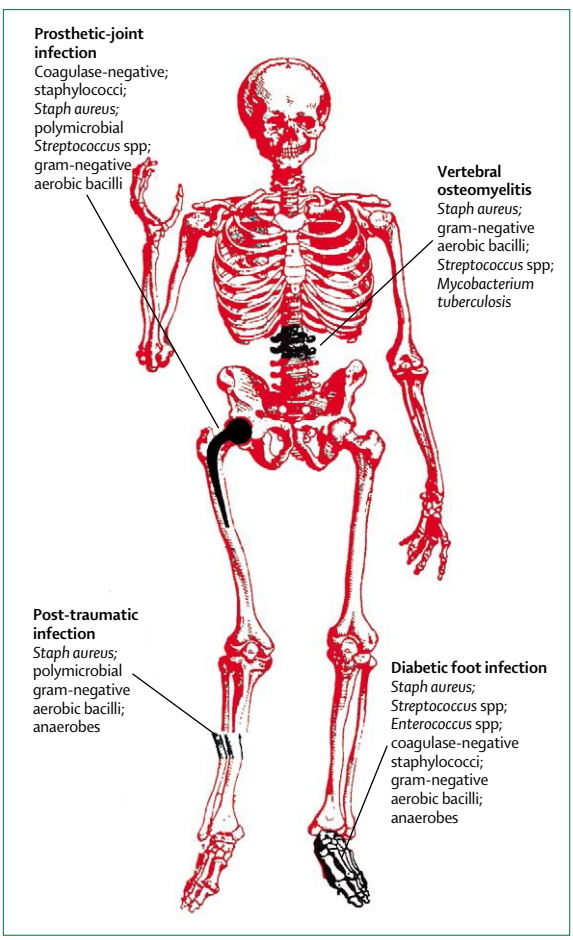

Figure 2: **Microbiology in various types of osteomyelitis**
Microorganisms are ranked from high to low prevalence or relative epidemiological importance.

attachment to extracellular matrix proteins, called bacterial adhesins. The ability of *Staph aureus* to adhere is thought to be crucial for the early colonisation of host tissues, implanted biomaterials, or both. *Staph aureus* expresses several adhesins (MSCRAMM, microbial surface components recognising adhesive matrix molecules) on its surface, each specifically interacting with one host protein component, such as fibrinogen, fibronectin, collagen, vitronectin, laminin, throm-bospondin, bone sialoprotein, elastin, or von Willebrand factor.[12] The second set of factors promote evasion from host defences (protein A, some toxins, capsular polysaccharides). The third set promote invasion or tissue penetration by specifically attacking host cells (exotoxins) or degrading components of extracellular matrix (various hydrolases). Finally, the ability of *Staph aureus* to invade mammalian cells may explain its capacity to colonise tissues and to persist after bacteraemia.[13] *Staph aureus* can promote its endocytic uptake by epithelial or endothelial cells. *Staph aureus* that has been internalised by cultured osteoblasts can survive within the cells.[14] Intracellular

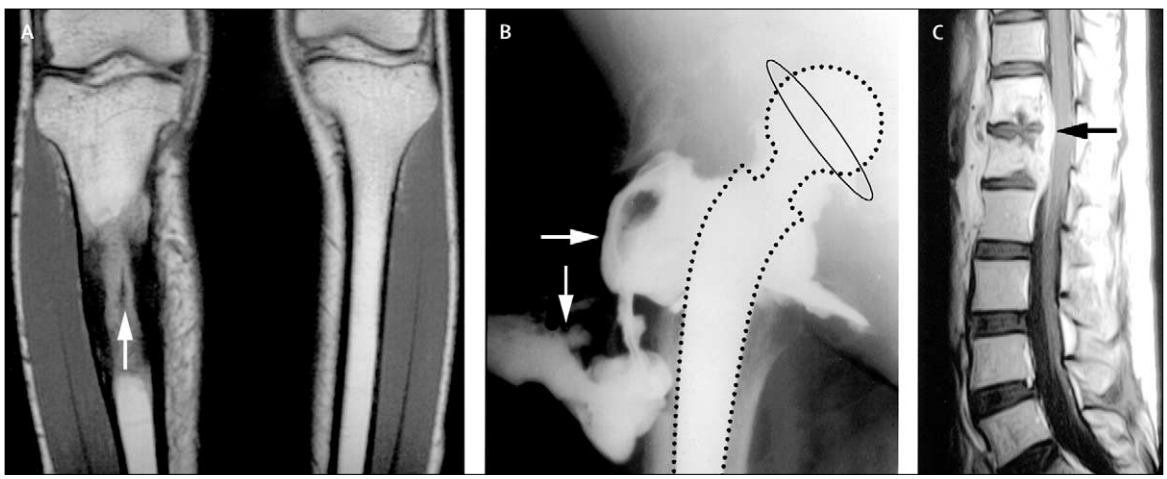

Figure 3: **Imaging procedures in osteomyelitis**
A: Chronic osteomyelitis—SE T1-weighted MRI, coronal view of both legs (for comparison) after intravenous injection of gadolinium-DPTA, shows cortical thickening, bone-marrow oedema, and a sequestrum (arrow) on the right tibia. B: Infected total hip prosthesis—in cases of suspected prosthetic infection, articular fluid is aspirated before surgery for bacterial culture; this is followed by dye injection for better visualisation of the articular space and possible fistula. In this case, arthrography shows a large periprosthetic abscess filled by contrast medium (arrows). The hip prosthesis is delineated. C: Vertebral osteomyelitis—MRI, sagittal view on SE T1-weighted after intravenous injection of gadolinium-DPTA, shows on vertebrae Th12–L1 high-signal intensity of the bone marrow and an epidural phlegmon (arrow). Images were provided by Prof Jean Garcia, Department of Radiology, University of Geneva Hospitals.

survival (sometimes in a metabolically altered state in which they appear as so-called small-colony variants) could explain the persistence of bone infections.[15,16] Many of these virulence factors have been cloned, sequenced, and physically located on the chromosome map of *Staph aureus*.[17,18]

Staph aureus and *Staph epidermidis* can also form biofilms, which are difficult to treat with antimicrobial agents.[19] A biofilm is a microbial community characterised by cells that attach to substratum or interface or to each other, embedded in a matrix of extracellular polymeric substance, and showing an altered phenotype in terms of growth, gene expression, and protein production.[20] Bacteria communicate with each other in biofilms through small hormone-like compounds, and this cell-to-cell signalling system is called quorum sensing. Biofilms can act as a diffusion barrier to slow down the penetration of antimicrobial agents and nutrients.

The inherent resistance of biofilms to antimicrobial factors seems to be mediated by several factors including low metabolic rates, adaptive stress responses, and downregulated rates of cell division of the deeply embedded microbes. Detection of differential gene expression and proteomes in biofilm-forming versus planktonic populations of *Staph aureus* is now providing a much better insight into the role of biofilms in osteomyelitis and prosthetic infections and could be the target for the development of new chemotherapeutic agents.[21–28]

Diagnostic procedures

Patients can present with a variety of symptoms ranging from an open wound exposing fractured bone, an indolent draining fistula, to no skin lesion, but local swelling and bone pain tenderness on clinical examination. Confirmation of osteomyelitis requires several diagnostic procedures as described below.

Microbiology and histopathology

In osteomyelitis of any kind, the most important step is to isolate the offending organisms so that the appropriate antimicrobial therapy can be chosen. Isolation can be achieved by blood cultures, generally only in haematogenous osteomyelitis, or by direct biopsy from the involved bone.[29,30] Bone biopsy has to be done under regional or general anaesthesia in some patients, but its importance cannot be overemphasised. Material taken from an open sinus tract by swabbing will give misleading results because the isolates may include non-pathogenic microorganisms that are colonising the site. Whenever bone biopsies are done, the samples should be processed for aerobic and anaerobic cultures. Samples for mycobacterial and fungal cultures should be taken and processed if commonly cultured microorganisms are not present and if the clinical features are compatible. In implant-associated infections, for maximum diagnostic yield, deep specimens should be obtained from up to five sites around the implant at debridement. Tissue specimens obtained for histopathology either by biopsy or during surgery as frozen section are also important because the presence of neutrophils in significant amounts is indicative of infection. More than five neutrophils per high-power field indicates infection, with sensitivity of 43–84% and specificity of 93–97%.[31,32] Visualisation of granulatomatous lesions with positive Ziehl-Neelsen staining leads to the diagnosis of mycobacterial infection earlier than culture results.

Although *Staph aureus* is the most commonly isolated microorganism in most types of osteomyelitis, many other microorganisms are isolated according to the type of disease and epidemiological factors (table 1, figure 2).

Laboratory studies

The white-blood-cell count is not a reliable indicator and can be normal even when infection is present. The erythrocyte sedimentation rate is high in most cases, but its kinetics are too slow for follow-up in osteomyelitis. The concentration of C-reactive protein, synthesised by the liver in response to any infection, appears more reliable for follow-up of the response to treatment. The concentration increases within hours of infection and returns to normal within a week after adequate treatment has begun in most cases.[33] However, both C-reactive protein concentration and erythrocyte sedimentation rate may be higher than normal for reasons other than osteomyelitis. Concentrations of calcium, phosphate, and alkaline phosphatase are normal in osteomyelitis, in contrast to metastatic or some metabolic bone diseases.

Imaging procedures

The diagnosis of skeletal infection entails a variety of imaging methods, but conventional radiography is necessary at both presentation and follow-up. Plain films show soft-tissue swelling, narrowing or widening of joint spaces, bone destruction, and periosteal reaction. Bone destruction, however, is not apparent on plain films until after 10–21 days of infection.[34–36] Ultrasonography can be useful for early diagnosis in acute osteomyelitis or for detection of a purulent collection in soft tissue.[37,38]

Both CT and MRI have excellent resolution power and can reveal the destruction of medulla as well as periosteal reaction, cortical destruction, articular damage, and soft-tissue involvement, even when conventional radiographs are normal (figure 3). CT is prone to image degradation owing to artefacts caused by the presence of bone or metal but is nevertheless useful for guiding needle biopsy.[39] In addition, CT provides excellent definition of cortical bone and a fair assessment of the surrounding soft tissues. It is especially useful in identification of sequestra. MRI, however, is more useful than CT for soft-tissue assessment. MRI also reveals early bony oedema and is therefore most useful for early detection of infection. However, although MRI is very sensitive, it is not helpful in assessing the response to therapy, given the persistence of bone-marrow oedema for many months despite microbiological cure.

Various radiopharmaceuticals are currently used for bone scintigraphy. Methylene diphosphonate binds to sites of increased bone metabolic activity and is highly sensitive in the early detection of acute osteomyelitis. Leucocyte scanning with radiolabelled blood cells (leucocytes or granulocytes labelled with indium-111 or technetium-99m) or specific antibodies has been used for imaging of infection with reported high sensitivity, and especially specificity, but it is less commonly used.[40–43] The limited specificity of routine bone scintigraphy should be mentioned because diabetic (Charcot) arthropathy, gout, trauma, and surgery can give false-positive results.

In positron emission tomography (PET) with fluorine-18-fluoro-D-deoxyglucose (FDG), uptake of the agent occurs in inflammatory cells (macrophages and leucocytes). FDG PET combined with CT scan appears particularly promising for delineation of lesions and their concomitant inflammatory or infectious activity.[44,45]

Osteomyelitis secondary to a contiguous infection

Chronic osteomyelitis, characterised by infected dead bone and in most cases poor local vascularisation within a compromised soft-tissue envelope, is difficult to eradicate. Systemic symptoms generally subside, but one or more foci in the bone still contain infected tissue, or a sequestrum. The infected foci within the bone are surrounded by sclerotic, avascular bone covered by a thickened periosteum and scarred muscle and subcutaneous tissue. This avascular envelope makes systemic antibiotics essentially ineffective. Intermittent exacerbations can occur for years and can respond temporarily to antibiotics (figure 1).

If the radiograph is positive (figure 3A) for osteomyelitis, the clinician should generally proceed directly to bone biopsy for identification of the infecting microorganism and its antimicrobial susceptibility. False-negative results can be obtained because osteomyelitis has a patchy distribution in bone.

Infection of bone lesions not covered by skin is common. However, these lesions can be colonised by bacteria that are not acting pathogenically. The results of sinus-tract cultures do not usually correlate with those of cultures obtained at bone biopsy but can be useful, particularly when *Staph aureus* is isolated.[46]

Osteomyelitis secondary to vascular insufficiency and diabetic foot infection

An estimated 15% or more of patients with diabetes will have a foot problem during their lifetime, and in a small but important proportion limb amputation will eventually be necessary.[6] The suspicion of osteomyelitis should be raised in diabetic patients with soft-tissue inflammation or skin ulcerations in the feet present for a week or longer, especially if the lesions are on bony prominences. Generally, patients have no fever and few signs of inflammation. Physical examination should include careful assessment of the vascular supply to the affected limb and of any concomitant neuropathy. The extent of vascular compromise can be assessed by transcutaneous oximetry (once inflammation has been

controlled) and by measurements of pulse pressure with doppler ultrasonography. If severe ischaemia is suspected, arteriography, including examination of the foot vessels, should be undertaken. Osteomyelitis is present when bone is exposed in the ulcer bed before or after debridement, or if a gently advanced sterile surgical probe reaches bone.[6,47] The likelihood of osteomyelitis is also greater with large or deep ulcerations. Large amounts of pus can be clinically undetected in the planes and spaces of the foot. In a case of suspected early bone infection in which the clinical presentation and examination do not establish the diagnosis and the results of plain-film radiographs are still normal, MRI can permit the detection or exclusion of early infection. Changes on plain radiographs are a later finding.

Microbiological diagnosis is best made by bone biopsy. For digits or small bones, a needle aspirate can be a helpful alternative. Several pathogenic bacteria can be isolated. *Staph aureus* still predominates, but other gram-positive or gram-negative aerobic or anaerobic bacteria should be considered, because infection is the only reversible process in many cases of this multifactorial disease (figure 2).

Osteomyelitis associated with an infected prosthesis

Because of the increasing numbers of implantations, infections associated with prostheses have become more common. More than a million hip replacements are done each year worldwide, and the number of other artificial joints (knees, elbows) inserted is also rising. Several experimental studies and early clinical experience have shown the high susceptibility to infection after insertion of prosthetic devices, even when microorganisms of low pathogenicity, such as *Staph epidermidis* or *Propionibacterium* spp, are present.[12] There is general agreement that for hip surgery, an infection rate of less than 1% should be achievable; for other joints the rate is higher because of their proximity to the skin surface and the more limited experience in joint design. The risk of infection is highest during the first 2 years after implantation but persists at lower levels as long as the prosthesis remains in place.[32] The economic burden to health-care systems associated with septic prosthetic joints is very high and has been calculated to be 5·3–7·2 times higher than for the primary operations.[48] Prosthesis removal, which is necessary for cure in most cases, produces large skeletal defects, shortening of the limb, and severe functional impairment. Thus, the patient faces protracted stays in hospital, much financial expense, and, most distressingly, renewed disability and even death.

Most patients have little or no fever and present with a painful, unstable joint on physical examination or radiography, most commonly within the first few years after implantation. Because of the difficulty in distinguishing mechanical from infectious loosening, a positive culture of fluid aspirated from the artificial joint space preoperatively (figure 3B) or of bone (also for histopathology) from the bone-cement interface during surgery is required for diagnosis. Cultures of several samples obtained from deep tissues are also useful. *Staph aureus* or coagulase-negative staphylococci account for more than 50% of the bacteria cultured (figure 2).

Other types of osteomyelitis

The diagnosis of underlying bone infection in a pressure sore should be considered whenever it does not heal with conventional local treatment or after removal of pressure.[49,50] However, clinical assessment of the depth of the sore or its duration is not helpful in decisions on whether bone infection is present. Bone scintigraphy is generally useful because of its high negative predictive value (>90%), although the positive predictive value is only around 80%.[42,43] Gram-negative bacilli, anaerobes, and streptococci are most commonly cultured from infected bone. Histology and culture of bone biopsy samples are the diagnostic gold standard; bone biopsy is rarely associated with complications.

Various exceptional clinical situations should be kept in mind. First, involvement of the sternoclavicular joint area has been described in intravenous-drug users and patients with indwelling intravenous devices. Second, osteomyelitis of the calcaneus, commonly caused by *Pseudomonas aeruginosa*, can follow apparently innocent puncture wounds. Third, osteomyelitis of the sternum, frequently due to coagulase-negative staphylococci, can follow cardiac surgery. Fourth, acute multifocal osteomyelitis is associated with skin disorders such as acne conglobata or palmoplantar pustulosis and is characterised by negative bone cultures and spontaneous healing over a period of several months. Lastly, although musculoskeletal complications of AIDS are less common than thoracic or cerebral infections, osteomyelitis is the most common musculoskeletal complication in patients with HIV infection or AIDS.[51]

Haematogenous osteomyelitis

Historically, haematogenous osteomyelitis has been described in prepubertal children. It involves mostly the metaphysis of long bones (particularly tibia and femur), in most cases as a single focus. Although rare in adults, it most frequently involves the vertebral bodies.

Bacteria causing this form of osteomyelitis (figure 2) reflect essentially their frequency in blood as a function of age.[52,53] Thus, organisms most commonly encountered in neonates and infants include *Staph aureus*, group-B streptococci, coagulase-negative staphylococci, and various streptococci (table 1).[52,54–56] Later in life, *Staph aureus* predominates; in elderly people, who are commonly subject to gram-negative bacteraemias,

vertebral osteomyelitis can also be caused by gram-negative bacilli.[57,58]

The clinical features of haematogenous osteomyelitis in long bones are typical: chills, fever, and malaise reflect the bacteraemic spread of microorganisms as shown by positive blood cultures; pain and local swelling are the hallmarks of the local infectious process. Clinical examination should include a search for bone tenderness.

Vertebral osteomyelitis

Vertebral osteomyelitis is most frequently of the haematogenous type and generally involves the lower dorsal or lumbar spine; involvement of the cervical spine is a rare, but well-described, clinical entity.[59] The disease mostly presents in adults as a febrile lumbago or torticollis. An arterial route[5] is believed to be the most likely route of infection: since the segmental arteries supplying the vertebrae generally bifurcate to supply both adjacent bony segments, the disease involves two adjacent vertebrae and subsequently their intervertebral disc. In some patients, at least, inflammation of the disc occurs before vertebral infection.[5] Plain radiographs are normal on admission, but abnormalities by bone scintigraphy or MRI are early clues to the diagnosis and appear within days; later, narrowing of the disc space, mottled destruction of adjacent vertebral plateaus, and anterior bridging are observed (figure 3C).

Because many organisms can cause this type of disease, needle biopsy under CT guidance has become the diagnostic procedure of choice. In addition to aerobic and anaerobic bacterial cultures, the samples should be sent for fungal and mycobacterial culture as well as for histology. If the first set of cultures is negative, an open surgical biopsy should be considered before therapy is started. Complications, including soft-tissue extension, paraspinal abscess, and cord compression have to be regularly watched for; emergency decompression may be dictated by the clinical and radiographic findings.

Skeletal tuberculosis

The haematogenous spread of *Myobacterium tuberculosis* early in the course of a primary infection can lead to skeletal tuberculosis. Rarely, it is a contiguous infection from an adjacent caseating lymph node. Any bone can be involved in skeletal tuberculosis, but the infection generally involves one site. In children and adolescents, the metaphysis of a long bone is most frequently infected. In adults, the axial skeleton is most commonly involved, followed by the proximal femur, knee, and small bones of the hands and feet. In the axial skeleton, the thoracic vertebral bodies are the most frequent site, followed by the lumbar and cervical vertebral bodies. Vertebral infection generally begins in the anterior portion of a vertebral body and is adjacent to an intervertebral disc. The infection produces destruction of the nearby bone and the intervertebral disc. Adjacent vertebral bodies can become involved, and a paravertebral abscess might develop. Tubercular spondylitis progresses slowly over years. 60% of patients with skeletal tuberculosis have evidence of extraosseous tuberculosis.[60]

Tissue for culture and histology is almost always required for the diagnosis of skeletal tuberculosis. Cultures for *M tuberculosis* are positive in about 60% of patients. But since weeks may be required for the growth and identification of the organism,[61,62] granulomatous tissue with positive Ziehl-Neelsen staining is sufficient for therapy to begin. Treatment for skeletal tuberculosis involves long courses of chemotherapy and in some cases surgical debridement.

Medical management of osteomyelitis

General principles in prevention and treatment of osteomyelitis

Antibiotic prophylaxis has been used successfully to prevent wound infections after surgery for non-compound hip fractures[63,64] and in the placement of total hip and knee prostheses. Standard preoperative preparations (including antimicrobial shower, shaving, and soap-disinfectants),[65] the use of surgical rooms with laminar air flow,[66,67] and prophylactic antibiotic treatment have decreased the infection rate after the placement of prostheses to 0·5–2·0% depending on the type of joint replacement.

In patients undergoing clean bone surgery, antibiotics should be administered intravenously from 30 min before skin incision[68] to no longer than 24 h after the operation. In surgery for closed fractures, antistaphylococcal penicillins or first-generation (cefazolin), or second-generation (cefamandole and cefuroxime) cephalosporins decrease the rates of postoperative infection.

Open fractures[69–72] are a special case. In patients who can receive antibiotics within 6 h of injury and who receive prompt operative treatment, administration of antistaphylococcal penicillins or first-generation or second-generation cephalosporins for 24 h is appropriate. Antimicrobial therapy should be followed by close observation and treatment with appropriate antibiotics and surgery if postoperative infection is diagnosed. Complex fractures with extensive soft-tissue damage require broader antibiotic therapy for longer periods.

A combined antimicrobial and surgical approach should be considered in all cases of osteomyelitis; whereas for haematogenous osteomyelitis surgery is generally unnecessary, at the other end of the range of disease (eg, an infected fracture), cure can be achieved with little antibiotic treatment provided that necrotic bone and foreign material is removed. In any case, if signs of infection do not abate after a week of antibiotic therapy, possible complications should be considered,

such as the presence of a subcutaneous, subperiosteal, or intramedullary abscess, the formation of sequestra, or the presence of foreign material. In most cases, surgical intervention solves this problem more radically than a switch to other antibiotics, provided that adequate microbiological results have led to appropriate initial antimicrobial chemotherapy.[73]

Selection of antimicrobial therapy and routes of administration

Antimicrobial therapy is adequate for the treatment of most cases of acute osteomyelitis of any type. A conventional choice of antimicrobial agents for the most commonly encountered microorganisms is given in table 2.[7,74,75] Single-agent antimicrobial therapy is generally adequate for the treatment of osteomyelitis except for infections of prosthetic joints (for which an antimicrobial combination including rifampicin is commonly used) and chronic osteomyelitis. As a general principle, these antibiotics should be given for 4–6 weeks, if possible by the intravenous route. Where quinolones are used, an early switch to oral administration is appropriate.

Clindamycin has excellent bone penetration and oral bioavailability; it is recommended for long-term oral therapy in infections with susceptible organisms, either alone or in combination. The fluoroquinolones have gained popularity in recent years because of their excellent oral bioavailability; they are efficient in experimental infections and in selected infections in adults.[76,77] Although their efficacy against *Enterobacteriaceae* is undisputed, an advantage over conventional therapy for infections with *Pseudomonas aeruginosa*, *Serratia* spp, and *Staph aureus* has yet to be shown in controlled studies.

The treatment currently recommended for osteomyelitis caused by *Staph aureus* is a long course of a parenterally administered semisynthetic penicillin or vancomycin. However, this treatment carries risks of complications associated with a long stay in hospital and adverse events due to the use of intravenous catheters, as well as associated personal and economic costs from the extended hospital stay. Several studies have shown that oral treatment with rifampicin in combination with ciprofloxacin, ofloxacin, or fusidic acid[78–81] is effective in bone staphylococcal infections in the presence of implants or prosthetic joints. We emphasise that the use of rifampicin in combination with quinolones is applicable only to organisms that are susceptible to both of these agents. The main advantage of the combination of quinolone and rifampicin is its excellent bioavailability, which allows oral administration, and the serum concentrations achieved are similar to those obtained during intravenous therapy. In addition, both drugs show good intracellular penetration and activity against intracellular and biofilm-associated staphylococci.[82–84] They can be given for long periods with good therapeutic results in chronic infections. Quinolones inhibit fracture healing, but the clinical significance of this observation is not known.[85] Parenteral therapy of *Staph aureus* osteomyelitis remains the approach of choice until more comparative studies are completed.

Microorganisms isolated	Treatment of choice	Alternatives
Penicillin-sensitive *Staph aureus*	Benzylpenicillin (12–20 million units daily)	Cefazolin (1 g every 6 h) Clindamycin (600 mg every 6 h) Vancomycin (1 g every 12 h)
Penicillin-resistant *Staph aureus*	Nafcillin* (1·0 or 1·5 g every 4–6 h) or cefazolin (2 g every 8 h)	Second-generation cephalosporin (eg, cefuroxime, cefamandole) Clindamycin (600 mg every 6 h) Vancomycin (1 g every 12 h) Ciprofloxacin (750 mg orally every 12 h) or levofloxacin in combination with rifampicin (600 mg per day) is also frequently used
Meticillin-resistant *Staph aureus*†	Vancomycin (1 g every 12 h)	Teicoplanin (400 g every 24 h, first day every 12 h)
Various streptococci (group A or B β-haemolytic; *Strep pneumoniae*)	Benzylpenicillin (12–20 million units daily)	Clindamycin (600 mg every 6 h) Erythromycin (500 mg every 6 h) Vancomycin (1 g every 12 h)
Enteric gram-negative bacilli	Quinolone (eg, ciprofloxacin, 400–750 mg every 12 h, with early switch to oral)	Third-generation cephalosporin (eg, ceftriaxone 2 g every 24 h; cefepime)
Serratia sp; *Pseudomonas aeruginosa*	Piperacillin‡ (2–4 g every 4 h) and aminoglycosides	Cefepime 2 g every 12 h‡ or a quinolone and aminoglycosides (according to sensitivity, one daily dose)
Anaerobes	Clindamycin (600 mg every 6 h)	Ampicillin-sulbactam (2 g every 8 h) Metronidazole for gram-negative anaerobes (500 mg every 8 h)
Mixed infection (aerobic and anaerobic microorganisms)	Ampicillin-sulbactam (2–3 g every 6–8 h)§	Imipenem (500 mg every 6 h)¶

All doses are given for normal renal/hepatic function and should be adjusted in renal or hepatic failure. Treatment is intravenous unless stated otherwise. Teicoplanin is presently available only in Europe. *Flucloxacillin, oxacillin, or cloxacillin in Europe. †Most coagulase-negative staphylococci are meticillin-resistant and treated with vancomycin or teicoplanin. ‡Depends on sensitivities; a fourth-generation cephalosporin (cefepime), piperacillin/tazobactam, meropenem, and imipenem are useful alternatives. §Amoxicillin-clavulanate in Europe (1·2–2·2 g every 6–8 h). ¶In cases of aerobic gram-negative microorganisms resistant to amoxicillin-clavulanate.

Table 2: **Antibiotic treatment of osteomyelitis in adults**

In haematogenous osteomyelitis of childhood, shorter courses of parenterally administered antibiotics followed by oral therapy for several weeks give an equal success rate; provided that the organism is known and adherence with treatment is good, the clinical signs abate rapidly.[86,87]

Several studies have shown the effectiveness of long-term oral therapy in adult chronic osteomyelitis; most of these studies used trimethoprim-sulfamethoxazole (co-trimoxazole) or quinolones, and the duration of therapy ranged from 6 weeks to 24 weeks.[77,88]

Another approach that has gained acceptance because of its lower cost is parenteral administration of antibiotics on an outpatient basis.[73,89] Ceftriaxone penetrates bone at about 10–20% of serum concentrations (as do other beta-lactams). Administration of ceftriaxone intravenously gives very high serum concentrations, so the concentrations in bone far exceed the minimum inhibitory concentration of susceptible isolates. The long serum and bone half-life allow once-daily dosing, a useful feature for outpatient parenteral therapy. This convenience makes inclusion of

ceftriaxone for *Staph aureus* bone infection useful, although it is not a primary agent for this indication and has a broader range than is desirable.[73] Nosocomial infections with meticillin-resistant *Staph aureus* (MRSA) or multidrug-resistant gram-negative bacilli necessitate long-term intravenous therapy with glycopeptides or broad-spectrum antibiotics (table 2).[90] For this purpose, continuous perfusions of vancomycin in the setting of outpatient parenteral therapy are a promising approach in MRSA osteomyelitis.[91,92] Linezolid is a new agent for MRSA, but experience is limited in osteomyelitis.[93–96]

Surgical management of osteomyelitis

Chronic osteomyelitis

Chronic osteomyelitis generally cannot be eradicated without surgical treatment. The goal of surgery is to achieve a viable vascularised environment and eliminate dead bone, which acts as foreign material. Radical debridement down to living bone is required to achieve this aim in many cases. Inadequate debridement is one cause of high recurrence rates in chronic osteomyelitis. Surgery for chronic osteomyelitis consists therefore of removal of sequestra and resection of scarred and infected bone and soft tissue.[97,98] When consolidation of a fracture has not yet occurred, full mechanical recovery can be achieved despite sepsis with local fixation material (which can be removed after consolidation), complemented by a short course of antibiotics.

Adequate debridement can leave a large dead space that must be managed to prevent recurrence and a significant bone loss that might result in bone instability. Appropriate reconstruction of both the bone and soft-tissue defects may be needed. A detailed radiological assessment should be made. The curative procedure should be done by a team including expertise in infectious diseases, radiology, orthopaedic surgery, and plastic surgery, especially of coverage techniques, such as skin grafts, muscle and myocutaneous flaps, and free flaps.[99]

Several techniques have been successful when properly carried out, but they require meticulous surgical technique.[100] The methods described to eliminate dead space can be summarised in five groups. The first is bone grafting with primary or secondary closure with cancellous bone that can quickly become revascularised; the bone fragments can also become incorporated into the final bone structure. In the Papineau technique, the wound is left open after bone grafting to allow the growth of granulation tissue before closure. These grafting procedures still have a substantial failure rate owing to resorption of the bone graft in the presence of persistent local infection. The second approach is use of antibiotic polymethylmethacrylate beads as a temporary filler of the dead space before reconstruction. Third, use of grafting of local muscle flaps and skin with or without bone-revascularisation procedures is the best means of fighting recurrent infection and approaches involving local pedicle muscle flaps and myocutaneous flaps are now those most frequently used. Local muscle flaps are limited by the availability of adjacent muscle but provide an intact vascular supply. Myocutaneous flaps have the advantage of providing vascular supply to both the muscle and the overlying skin. Increasingly, microsurgically transplanted (or free-tissue) muscle flaps are being used in areas such as the distal tibia where there is no appropriate muscle. The last two approaches are microvascular transfer of muscle and myocutaneous, osseous, or osteocutaneous flaps and the use of bone transport to fill large bone defects and avoid amputations. In the Ilizarov technique,[101,102] the resection of diseased tissue and bone creates a gap partially filled by a well-vascularised bone segment. Transfer of the bone graft leads to progressive local generation of new bone. This is a complex and expensive procedure, more popular in Europe than in the USA.[1] Alternatively, recent experience with the microvascular transfer of fibular grafts and composite osteocutaneous iliac flaps into infected areas of bone has shown that massive autogenous bone grafting with an intact vascular pedicle decreases the time needed for bone union and shortens the period of immobilisation.

Vertebral osteomyelitis

Surgical intervention is limited to the management of complications or for therapy failure. It is undertaken mainly to relieve compression of the spinal cord or to drain epidural or paravertebral abscesses and to improve spinal stability.

Diabetes foot infection

The treatment depends on the vascularisation of tissue at the infected site, the extent of local infection, and the patient's preference.[96] Surgery to restore vascularisation can be useful before amputation is considered. Long-term oral antibiotic suppression to delay or obviate amputation is also an option. There is no definitive evidence that hyperbaric oxygen is effective in this setting. Debridement and a 4–6-week course of antimicrobial therapy can benefit a patient who has good oxygen tension at the infected site, particularly if the identity of the pathogen has been established.[103] In the absence of good oxygen tension, the wound fails to heal, and amputation of the infected foot is eventually necessary. Resection of chronic osteomyelitic bone is therefore frequently used. Choices are digital resection, transmetatarsal amputation, and disarticulation at the midfoot, with the aim of allowing the patient to walk without an orthosis.

Prosthetic-joint infections

Treatment depends on the anatomical location of the prosthesis and the type of underlying disease. The basic

rule is to remove the device. A classic approach for prosthetic infection, well documented for hip infections and by extension for other prosthetic joints, is a two-stage exchange arthroplasty. It entails the surgical removal of all foreign material, debridement of the bone and soft tissues, and 4–6 weeks of parenteral antimicrobial therapy before reconstruction.[104] In one-stage exchange arthroplasty, a new prosthesis is immediately inserted. Practitioners of the one-stage technique always use cement containing an antimicrobial drug, which may contribute to the high success rate reported with this procedure. Nevertheless, one-stage arthroplasty carries a higher risk of recurrent infection than the two-stage procedure and is used only in hip prosthetic infection.[31] For other prosthetic joints (knee, shoulder, elbow), two-stage exchange with the use of antibiotic-loaded cement is preferred.

Exceptions to exchange arthroplasty, allowing cure with antibiotics alone and leaving the prosthetic material locally, include situations involving a stable hip prosthesis infected with very sensitive microorganisms such as streptococci or the early diagnosis of device-related infections with staphylococci, which have been reported to be cured by debridement alone followed by several months of treatment with oral quinolones and rifampicin.[48,81] This approach has been particularly useful in elderly patients because of their higher morbidity and mortality, particularly morbidity secondary to exchange arthroplasty surgery and concomitant long hospital stays.[48,92]

Conclusions

Greater awareness, new diagnostic methods, and better treatment for people with ready access to modern health care have led to a decrease in the rate of treatment failure in acute osteomyelitis. Sequelae have become less frequent. Infection control strategies and prophylactic antibiotics have further lowered the rate of postoperative infection. However, the large increase in reconstructive orthopaedic procedures with prosthetic materials will increase the overall number of infections, because no preventive measure is likely to lower the rate of infections below 0·5%. New materials for reconstruction are needed to combine excellent mechanical with bacterial antiadhesive properties and to approximate more closely the extracellular matrix. In chronic osteomyelitis, new surgical approaches combining orthopaedic, plastic surgery, and vascular techniques are necessary. Further research is also required to identify new biological factors that promote bone growth, to allow more rapid new bone formation, shorten the period of vulnerability to infection, and permit faster recovery after surgery.

Osteomyelitis entails a major financial burden and substantially affects quality of life. An open dialogue between patient and doctor is essential in the treatment of this disease, based on a clear medical understanding of the risks, costs, and chances of success of treatment options.

Conflict of interest statement

None declared.

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