The host and the skeletal infection: classification and pathogenesis of acute bacterial bone and joint sepsis

Jon T. Mader MD
Professor
Department of Internal Medicine and Pathology; Chief, Section Surgical Infectious Diseases; Adjunctive Professor, Department of Orthopedic Surgery; and Chief of Marine Medicine, Marine Biomedical Institute, University of Texas Medical Branch, Galveston, Texas, USA

Mark Shirtliff BS
Research Director
Division of Marine Medicine, Marine Biomedical Institute; a Graduate Student, Department of Microbiology and Immunology, University of Texas Medical Branch, Galveston, Texas, USA

Jason H. Calhoun MD
Professor
Director of the Department of Orthopedic Surgery, Adjunctive Member, Marine Biomedical Institute, University of Texas Medical Branch, Galveston, Texas, USA

Bone and joints are normally sterile areas. Bacteria may reach these sites by either haematogenous spread or spread from an exogenous or endogenous contiguous focus of infection. Bone infection, or osteomyelitis, is characterized by a progressive infectious process resulting in inflammatory destruction of bone, bone necrosis and new bone formation. Joint infections, or infectious arthritis, arise either from the haematogenous spread of organisms through the highly vascularized synovial membrane or from direct extension of a contiguous bone or soft tissue infection. The most commonly involved joints are the knee and the hip, although any joint can become infected. Infectious arthritis is monoarticular in 90% of cases. Some of the questions to be answered in this chapter include: how bacteria reach and cause damage in the bones and joints; what the current classification systems of bone and joint infections are, what some risk factors and host factors associated with bone and joint infection are; what some current characteristics of musculoskeletal infections are and whether the damage to joints can be diminished by treatment.

Key words: Osteomyelitis; arthritis; bacterial arthritis; bone infection; skeletal infection; Waldvogel classification system; Cierny–Mader classification system; gonococcal arthritis; non-gonococcal arthritis; pathogenesis of osteomyelitis; pathogenesis of joint infection; Neisseria gonorrhoeae in joint infections; Staphylococcus aureus; Haemophilus influenzae; Pseudomonas aeruginosa; Serratia marcescens; Streptococcus spp.

0950-3579/99/010001 $12.00/00 © 1999, Baillière Tindall
OSTEOMYELITIS

Normal bone is highly resistant to infection, which occurs only as a result of a very large inoculation of organisms, trauma leading to bone damage, or the presence of foreign bodies. The pathogenesis of osteomyelitis has been explored clinically in various animal models and in vitro at the cellular and molecular biology levels. The pathogenesis of osteomyelitis is multifactorial and poorly understood. Virulence determinants of the organisms, underling disease, the immune status of the host and the type and location of the bone are some of the important factors. It is clear that bacterial cells adhere to nucleated cells, platelets and a variety of components of the extracellular bone matrix collagen and non-collagenous proteins.

Cellular and molecular pathogenesis of osteomyelitis

Cellular and molecular techniques provide new methods for determining the relative importance of the many potential virulence factors. These techniques allow study of the interaction between the host's immune response and potential virulence factors. *Staphylococcus aureus* is an important cause of both haematogenous and contiguous focus osteomyelitis. *Staphylococcus aureus* produces a large number of extracellular and cell-associated factors that may contribute to its virulence. The bacteria adhere to bone by expressing receptors for the components of bone matrix including fibronectin, laminin, collagen and bone sialoglycoprotein (Hermann et al, 1988; Yacoub et al, 1995; Ryden et al, 1997). Increasing evidence supports the importance of staphylococcal surface components as virulence determinants. Potential proteolytic activity present in normal joints remains inhibited in the absence of infection. In an in vitro model of adult chondrocytes inoculated with *S. aureus*, overall protein synthesis was inhibited by 84%, with an increased release of collagenase and gelatinase (Williams et al, 1990). In a mouse model, there was significant binding of *S. aureus* to bone sialoprotein, fibronectin and type I collagen, indicating that adherence remains a key phase in the early stages of infection (Bremell et al, 1991). The expression of adhesins permits the attachment of the pathogen to cartilage. The inoculation of mice with mutants positive and negative for the collagen adhesin gene showed that septic arthritis occurred in over 70% of mutant positive strains but in only 27% of the mutant negative strains (Switalski et al, 1993). Collagen adhesin-positive strains were also associated with the production of high levels of IgG and interleukin-6 (Switalski et al, 1993). It is speculated that bone infection might be prevented by a vaccine derived from adhesin. Fibronectin-binding protein rapidly coats any foreign body implanted in a patient and, in vivo, adheres to biomaterials coated with host proteins. An in vivo study of endocarditis with a rat model showed that mutants deficient for fibronectin binding protein were 250-fold less adherent to traumatized heart valves (Kuyers and Proctor, 1989). *Staphylococcus aureus* adherence to miniplates from the iliac bones of guinea pigs was three times higher than in the adhesin-defective mutant strain (Fischer et al, 1996). It is probable that fibronectin binding proteins play an important role in bone and joint infections, especially those associated with prosthetic joints (Gemmell et al, 1991).

The difficulty with treating osteomyelitis resides in the organism's defence mechanisms. Such characteristics are expressed at both the cellular and matrical levels. *Staphylococcus aureus* that has been internalized by cultured osteoblasts can survive intracellularly. The collagen-binding protein increases the likelihood of staphylococcal adherence. The presence of arachidonic acid metabolites, such as
prostaglandin E2, which is a strong osteoclast agonist, decreases the amount of the bacterial inoculum needed to produce infection. Once the micro-organisms adhere to bone, they express phenotypic changes that make them resistant to antimicrobial treatment.

*Staphylococcus aureus* organisms also express a 42 kDa protein, protein A, which is bound covalently to the outer peptidoglycan layer of their cell walls. Protein A binds to the Fc portion of IgG on polymorphonuclear leukocytes, interfering with their opsonization and phagocytosis. This interference has been demonstrated in vitro and in animal models with subcutaneous abscesses and peritonitis (Gemmell et al, 1991). *Staphylococcus aureus* also secretes enterotoxin and toxic shock syndrome toxin (TSST-1). Both enterotoxin and TSST-1 have been shown to exert a profound effect on the immune system when administered parenterally. They act as superantigens and suppress plasma cell differentiation. They also stimulate the production of cytokines such as interleukin (IL) (Nair et al, 1995), interferon gamma and tumour necrosis factor (TNF) (Littlewood-Evans et al, 1997). Animals infected with strains of *S. aureus* isogenic for TSST-1 developed frequent and severe arthritis (Schlievert, 1993). Protein A and capsular polysaccharide may interfere with opsonization and phagocytosis. Enterotoxin and TSST-1 subvert the cellular and humoral immune systems, which may determine whether a local infection is eliminated or develops into osteomyelitis or septic arthritis.

The increased turnover of bone in osteomyelitis suggests that the balance between bone formation and resorption may be mediated by nitric oxide. Greatly increased levels of nitric oxide and bone resorption have been recorded in the septic skeleton (Smith et al, 1998), perhaps driven by the increased levels of cytokines (IL; TNF, enterotoxin and TSST-1) acting to stimulate nitric oxide production by endothelial, macrophage and mesenchymal cells such as osteoblasts (Seledssova et al, 1997). Thus, while low levels of nitric oxide are classically thought to inhibit osteoclastic bone resorption protection may be lost in the instance of the cytokine and nitric oxide overload in skeletal inflammatory disease. Adjunctive local treatment of osteomyelitis with nitric oxide synthase inhibitors could be beneficial.

**Classification of osteomyelitis**

Bone infections are currently classified by Waldvogel et al’s, system (Lew and Waldvogel 1997; Waldvogel et al, 1970) as either haematogenous osteomyelitis or osteomyelitis secondary to a contiguous focus of infection. Contiguous focus osteomyelitis has been further subdivided into osteomyelitis with or without vascular insufficiency.

An alternative classification system has been developed by Cierny and Mader (Table 1) (Cierny et al, 1985; Cierny and Mader, 1994; Mader et al, 1997). This classification takes into consideration the quality of host, the anatomical nature of the disease, treatment factors and prognosis factors. This staging system combines four anatomical disease types and three physiological host categories thus defining 12 discrete clinical stages of osteomyelitis.

Stage 1, or medullary, osteomyelitis, equates with early haematogenous osteomyelitis in which the primary lesion is endosteal. Adult stage I osteomyelitis is usually treated with cortical unroofing and intramedullary reaming. An infected intramedullary rod in a stable bone is another example of stage I osteomyelitis. In this case, the infected intramedullary rod must be removed, followed by intramedullary reaming.
In stage 2, or superficial, osteomyelitis, the bone infection results from an adjacent soft tissue infection and represents a true contiguous focus lesion. An exposed, infected necrotic outer surface of the bone lies at the base of a soft tissue wound. Stage 2 osteomyelitis requires superficial debridement and coverage with a local or microvascular flap.

Stage 3, or localized, osteomyelitis is characterized by full-thickness cortical sequestration that can be surgically removed without compromising the stability of the infected bone. Stage 3 osteomyelitis requires debridement, saucerization and possibly a bone graft to improve stability.

Stage 4, or diffuse, osteomyelitis, represents a through-and-through section of the bone and usually requires segmental resection of the bone. The stage 4 patient may also have bone infection on both sides of a non-union or major joint. Diffuse osteomyelitis includes those infections with a loss of bony stability either before or after debridement surgery. Stage 4 osteomyelitis requires debridement, dead space management and stabilization.

In this system (Table 1) patients are classified as A, B or C hosts. A hosts are those patients with normal physiological metabolic and immunological capabilities. B hosts are patients who are locally or systemically compromised, or both. It is important to improve the factors and diseases that made the patient a B host. The goal of host modification is to make a B host as much like an A host as possible. The final category, that of the C host, represents the patient for whom the treatment of the bone infection is worse than the osteomyelitis itself. This staging system has been used to determine optimal treatment protocols and prognoses, and to
compare therapy results between institutions. The stages are dynamic and may be altered by therapy outcome or a change in host status.

The term 'cure' is not used in osteomyelitis since the bone infection may recur years after the apparently successful treatment of the disease. If the patient suffers trauma in the involved area and/or the host response to the infection is suppressed, the organism(s) may again proliferate and lead to an exacerbation of the infection. Therefore, in osteomyelitis treatment, the infection is said to be 'arrested' rather than 'cured'.

**Properties of osteomyelitis (based on the Waldvogel classification system)**

**Haematogenous osteomyelitis**

Haematogenous osteomyelitis is predominantly encountered in the paediatric population, 85% of cases being found in patients younger than 17 years of age. Haematogenous osteomyelitis accounts for 20% of all cases of osteomyelitis. Recent studies have documented a decline in the incidence of haematogenous osteomyelitis, especially in children (Espersen et al, 1991). In children, the bone infection usually affects the long bones, while in adults, the lesion is usually located in the thoracic or lumbar vertebrae. Haematogenous osteomyelitis is more common in males of any age.

The metaphyses of the long bones (tibial and femur) are most frequently involved, the anatomy of the metaphyseal region seeming to explain this clinical localization (Trueta and Morgan, 1960). The nutrient artery ends in the metaphyses as narrow capillaries that make sharp loops near the growth plate and enter a system of large venous sinusoids where the blood flow becomes slow and turbulent. These capillary loops are essentially the 'end-artery' branches of the nutrient artery. This structure leads to a slowing of blood flow in the area and presumably allows bacteria to settle and initiate an inflammatory response. The histology of the region may also contribute. The metaphyseal capillaries lack phagocytic lining cells, and the sinusoidal veins contain functionally inactive phagocytic cells (Hobo, 1922). This further allows the growth of micro-organisms. Any end-capillary obstruction could lead to an area of avascular necrosis. Minor trauma probably predisposes the infant or child to infection by producing a small haematoma, vascular obstruction and subsequent bone necrosis that is susceptible to inoculation from a transient bacteraemia (Morrissy and Haynes, 1984). Acute infection initially produces a local cellulitis that results in a breakdown of leukocytes, increased bone pressure, decreased pH and decreased oxygen tension. The cumulative effects of these physiological factors further compromise the medullary circulation and enhance the spread of infection. Infection may proceed laterally through the haversian and Volkmann canal system, perforate the bony cortex and lift the periosteum from the surface of the bone. When this occurs in the presence of medullary extension, the periosteal and endosteal circulations are compromised; capillaries are lost, and large segments of cortical and cancellous bone die. In infants, medullary infection may spread to the epiphysis and joint surfaces through capillaries that cross the growth plate. In the child over 1 year of age, the growth plate is avascular and the infection is confined to the metaphysis and diaphysis. The joint is spared unless the metaphysis is intracapsular. Thus cortical perforation at the proximal radius, humerus or femur enables the infection to migrate to the elbow, shoulder or hip joint, regardless of the age of the patient.
A single species of pathogenic organism is almost always recovered from the bone. Polymicrobial haematogenous osteomyelitis is rare (Waldvogel et al., 1970; Mader et al., 1996). In infants, *S. aureus*, *Streptococcus agalactiae* and *Escherichia coli* are the most frequently recovered bone isolates, while in the child, *S. aureus*, *Streptococcus pneumoniae* and *Haemophilus influenzae* are the organisms most commonly isolated. After the age of 4 the incidence of *H. influenzae* osteomyelitis decreases. However, the overall incidence of *H. influenzae* as a cause of osteomyelitis is decreasing because of the new *H. influenzae* vaccine now given to children (De Jonghe and Glaesener, 1995).

Infants and children have clinically different presentations of osteomyelitis. Neonatal osteomyelitis is characterized by a lack of systemic and local findings (Ish-Horowicz et al., 1992). Local findings include decreased movement of a limb and oedema. A joint effusion adjacent to the bone infection is present in 60–70% of cases. Classically, children with haematogenous osteomyelitis present with abrupt fever, irritability, lethargy and signs of local inflammation of 3 weeks or less in duration. However, 50% of children now present with vague complaints, including pain in the involved limb of 1–3 months duration and minimal temperature elevation. Infants and children with haematogenous osteomyelitis usually have normal soft tissue enveloping the infected bone and are capable of a very efficient metabolic response to infection. They also have the potential to absorb large sequestra and generate a significant periosteal response to the infection. This later feature leads to a substantial formation of bone called an involucrum at the margin of the infection. The involucrum affords skeletal continuity and maintains function during the healing phase. If antimicrobial therapy directed at the responsible pathogen is begun prior to extensive bone necrosis, there is excellent potential for an arrest of the infection.

Haematogenous osteomyelitis is also found in the adult population. Adults usually present with vague complaints consisting of non-specific pain and few constitutional symptoms of 1–3 months duration. However, acute clinical presentations of fever, chills, swelling and erythema over the involved bones are occasionally seen. The clinical signs resulting from soft tissue extension often dominate the findings at presentation and can lead to inappropriate diagnostic and therapeutic measures being taken unless the clinical suspicion of an osseous aetiology is entertained. The infection usually begins in the diaphysis but may spread to involve the entire medullary canal. Extension into the epiphysis and joint space may occur since the growth plate has matured and once again shares vessels with the metaphysis. As the periostium is firmly adherent to the bone, cortical penetration usually leads to a soft tissue abscesses. Subperiosteal abscesses and massive cortical devitalization occur rarely. In time, sinus tracts connecting the sequestrated nidus of infection to the skin via soft tissue extension may form.

Vertebral osteomyelitis in the adult population is usually haematogenous in origin but may be secondary to trauma. A preceding history of urinary tract infection or intravenous drug abuse is often present. Early involvement of the anterior–inferior edge of the vertebral body suggests spread from the bony entrance of the anterior spinal artery (Wiley and Trueta, 1959; Croke and Goldwasser, 1984). Retrograde infection via Batson's venous plexus is also postulated (Eaton, 1940). The segmental arteries supplying the vertebrae usually bifurcate to supply two adjacent bony segments. Therefore the disease usually involves two adjacent vertebrae and the intervening intervertebral disc. The lumbar vertebral bodies are most often involved, followed by the thoracic and cervical vertebrae. Spread to adjacent
vertebral bodies may occur rapidly through the rich venous network of the spine. Posterior extension may lead to epidural and subdural abscesses or even meningitis. Extension anteriorly or laterally may lead to paravertebral, retropharyngeal, mediastinal, subphrenic, retroperitoneal or psoas abscesses. The infection is usually monomicrobial when haematogenous in origin. In the normal host, S. aureus remains the most commonly isolated organism. However, aerobic Gram-negative rods are found in 30% of cases. Pseudomonas aeruginosa and Serratia marcescens display a high incidence in the intravenous drug users (Holzman and Bishko, 1971). Other sources of infection include the genitourinary tract, skin and soft tissue, the respiratory tract, an infected intravenous site, endocarditis, dental infection or unknown foci. Clinically, the patient usually presents with vague symptoms and signs, consisting of dull, constant back pain and spasm of the paravertebral muscles (Sapico and Montgomery, 1979). Localized pain and tenderness of the involved bone segments is present in at least 90% of cases. The pain is usually insidious and progresses slowly over 3 weeks to 3 months.

Contiguos focus osteomyelitis without generalized vascular insufficiency

Osteomyelitis secondary to contiguous foci of infection accounts for at least half all case. Two recent studies have documented a decline in haematogenous osteomyelitis accompanied by a rise in contiguous disease (Esperensen et al, 1991). The organisms may be directly inoculated into the bone at the time of trauma, spread by nosocomial contamination during peri-operative or intra-operative procedures, or extend from an adjacent soft tissue infection. Common predisposing factors include surgical reduction and internal fixation of a fracture, open fractures and chronic soft tissue infections. In age distribution, contiguous focus osteomyelitis is biphasic. The infection occurs in the younger individuals secondary to trauma and related surgery, and in older adults secondary to decubitus ulceration.

In contrast to haematogenous osteomyelitis, multiple organisms are usually isolated from the infected bone. Staphylococcus aureus and coagulase-negative Staphylococci account for 75% of the bacterial isolates (Mader et al, 1996). However, Gram-negative bacilli and anaerobic organisms are frequently isolated. The infection usually manifests within 1 month of inoculation of the organisms from trauma, surgery or a soft tissue infection. Patients usually present with low-grade fever, pain and drainage. Loss of bone stability, bone necrosis and soft tissue damage frequently occur, making this form of osteomyelitis difficult to treat.

Contiguos focus osteomyelitis with generalized vascular insufficiency

The majority of the patients placed into this category of osteomyelitis have diabetes mellitus. The small bones of the feet, talus, calcaneus and distal fibula, and the tibia, are commonly involved in this category of infection. The patients in this group range from 35 to 70 years of age. The infection is commonly initiated by minor trauma of the feet, such as infected nail beds, cellulitis or trophic skin ulceration. The diminished arterial blood supply has traditionally been considered to be the major predisposing factor, but recent observation suggests that neuropathy is equally important. Identifiable neuropathy as a complication of diabetes mellitus is present in approximately 80% of patients with foot disease (Caputo et al, 1994).

Neuropathy causes foot infection through via main mechanisms. First, patients with decreased sensation suffer mechanical or thermal injuries leading to skin
ulceration, without being aware of them. Second, motor neuropathy affecting the intrinsic muscles of the foot predisposes to gait disturbances and foot deformities such as hammer and claw toes, and Charcot foot. These anatomical alterations may lead to a maldistribution of weight, which elevates focal pressure over the bony prominences. The increase in focal pressure where the foot contacts the ground or footwear may lead to subsequent skin ulceration. Third, autonomic neuropathy also contributes by interfering with sweating and causing dry, cracked skin, which breaches the integrity of the skin envelope allowing micro-organisms to enter the soft tissue. All three mechanisms may cause skin ulceration with subsequent skin infection, which may lead to contiguous focus osteomyelitis. A higher rate of nasal and skin colonization with S. aureus, defects in host immunity and impaired wound healing all play role in diabetic foot infection. Superficial fungal skin infections, which are common in diabetic patients, may also allow the entry of bacteria through macerated or broken skin.

Multiple organisms are found in patients with diabetic foot osteomyelitis, including S. aureus, coagulase-negative Staphylococcus spp., Streptococcus spp., Enterococcus spp., Gram-negative bacilli and anaerobes. Aerobic Gram-negative bacilli are usually a part of mixed infection (Calhoun et al., 1988).

Osteomyelitis in vascularly compromised patients can be difficult to diagnose. The patient may present with a ingrown toenail, a perforating foot ulcer, cellulitis or a deep space infection. Concurrent peripheral neuropathy dulls the patient's perception of pain. Fever and systemic toxicity are often absent. Examination shows decreased dorsal pedis and posterior tibia pulses, poor capillary refill and decreased sensation. Although arrest of the infection is desirable, a more attainable treatment goal is to suppress the infection and maintain the functional integrity of the involved limb. Recurrent or new bone infection occurs in the majority of the patients even after appropriate treatment. Resection of the infected bone is almost always necessary.

Pathology of osteomyelitis

Pathogenic organisms reach the bones by direct extension from neighbouring infected soft tissues, through penetrating wounds and open fractures, or via the bloodstream. Acute osteomyelitis presents as a suppurative infection with acute inflammatory cells, accompanied by oedema, vascular congestion and small vessel thrombosis. In early acute disease, the vascular supply to the bone is compromised by infection extending into the surrounding soft tissue. When both the medullary and periosteal blood supplies are compromised, large areas of dead bone (sequestra) may be formed. Within this necrotic and ischaemic tissue, the bacteria may be difficult to eradicate even after an intense host response, surgery and/or antibiotic therapy. Both clinically and histologically, acute osteomyelitis blends into chronic disease. Pathological features of chronic osteomyelitis are necrotic bone, the formation of new bone and polymorphonuclear leukocyte exudation joined by large numbers of lymphocytes, histiocytes and occasional plasma cells.

The necrosis of normal tissue is an important feature of infection. Dead bone is absorbed by the action of granulation tissue developing at its surface. Absorption takes place earliest and most rapidly at the junction of living and necrotic bone. If the area of the dead bone is small, it is entirely destroyed by granulation tissue, leaving a cavity behind. The necrotic cancellous bone in localized osteomyelitis, even though extensive, is usually absorbed. Some of the dead cortex (cortical bone) is gradually
detached from the living bone to form a sequestrum. The organic elements in the
dead bone are largely broken down by the action of proteolytic enzymes elaborated
by host defence and mesenchymal cells, mainly polymorphonuclear leukocytes,
macrophages and osteoclasts. Because of lost blood supply, dead bone appears
whiter than living bone. Cancellous bone is absorbed rapidly and may be completely
sequestrated (separated) or destroyed in 2–3 weeks, but necrotic cortex may
require between 2 weeks and 6 months for its separation. After complete
sequestration, the dead bone is slowly eroded by granulation tissue and absorbed.

New bone formation is also a characteristic feature of osteomyelitis. New bone
forms from the surviving fragments of periosteum, endosteum and cortex in the
region of the infection and is produced by a vascular reaction to the infection. New
bone may be formed along the intact periosteal and endosteal surfaces. It may arise
from the periosteum, forming an encasing sheath of live bone—the involucrum—
surrounding the dead bone under the periosteum. The involucrum is irregular and is
often perforated by openings through which pus may track into the surrounding soft
tissues and eventually drain to the skin surfaces, forming a drain sinus tract. The
involucrum may gradually increase in density and thickness to form part or all of a
new shaft. New bone increases in amount and density for weeks or months, accord-
ing to the size of the bone and the extent and duration of infection. Endosteal new
bone may proliferate and obstruct the medullary canal. After host defence removal
or surgical removal of the sequestrum, the remaining cavity may be filled with new
bone, especially in children. However, in adults, the cavity may persist or the space
be filled with fibrous tissue, which may connect with the skin surface via a sinus
tract.

The surviving bone in the field of osteomyelitis usually becomes osteoporotic
during the active period of infection, osteoporosis being the result of the inflam-
matory reaction and atrophy disease. After subsidence of the infection and an
increase in function of the part, bone density returns, which may undergo extensive
transformation to meet the lines of stress and strain. In time, it may be difficult to
distinguish between the old living bone and the newly formed bone. In children, and
to a lesser extent adults, all traces of osteomyelitis may disappear.

There are basic differences in the pathological characteristic of osteomyelitis
between infants, children and adults. In infants, small capillaries cross the epi-
physeal growth plate and permit extension of the infection into the epiphysis and
joint space. The cortical bone of the neonate and infant is thin and loose, consist-
ing predominantly of woven bone, which permits the escape of pressure caused by
infection but also promotes the rapid spread of the infection directly into the sub-
periosteal region. A large sequestrum is not produced because extensive infarction
of the cortex does not occur, but a large subperiosteal abscess may form. In
children older than 1 year of age, infection presumably starts in the metaphyseal
sinusoidal veins and is contained by the growth plate. The joint is spared unless the
metaphysis is intracapsular. The infection spreads laterally, breaking through the
cortex and lifting the loose periosteum to form a subperiosteal abscess. In adults,
the growth plate has resorbed and the infection may again extend to the joint
spaces. Also in adults, the periosteum is firmly attached to the underlying bone, so
subperiosteal abscess formation and intense periosteal proliferation are less
frequently seen. The infection may erode through the periosteum, forming a
draining sinus tract(s). Adult haematogenous osteomyelitis localizes within the
cancellous bones, particularly the lumbar and thoracic areas of the spine, more
frequently than within the long bones.
JOINT INFECTIONS

Source of infection

Virtually every bacterial organism has been reported to cause septic arthritis. Most septic joints develop as the result of haematogenous seeding of the vascular synovial membrane. The synovial membrane has no limiting basement plate, allowing easy entry of bacterial organisms. Septic arthritis occurs rarely as a result of joint aspiration or joint injection. Bacterial arthritis has been reported secondary to penetrating trauma or after direct trauma to a joint without an obvious break in the skin. Also, when a bone infection breaks through the outer cortex and into the intracapsular region, joint infection can result.

Pathogenesis

The usual host response to joint infection is polymorphonuclear invasion of the synovial membrane of the infected joint. Host cells release inflammatory cytokines, including but not limited to IL-1β, TNF, IL-6 and granulocyte-macrophage colony-stimulating factor, which have been shown in animal models to be required for bacterial clearance and the prevention of mortality from bacteraemia and septic shock (Koch et al, 1996; Verdrengh and Tarkowski, 1998). Nitric oxide, the common mediator of inflammatory cytokines, is also required (Sakiniene et al, 1997). While a normal inflammatory response is required in the host response to joint infection, significant destruction of the infected joint can occur when the inflammatory response is hyperactivated. It has been noted in a number of studies that superantigens such as TSST-1 and enterotoxins A–D are primarily responsible for this overactivation of the host inflammatory response, thereby increasing the mortality rate and exacerbating host inflammatory cell invasion, cytokine release and joint degradation (Bremell and Tarkowski, 1995). Activated macrophages release proteolytic enzymes, leading to the destruction of intra-articular cartilage in as little as 3 days. During acute experimental bacterial arthritis in animals, the cytokines elaborated by the host macrophages, including IL-1 and TNF, degrade cartilage by the induction of stromelysin and other metalloproteinases. When these factors are attenuated by monoclonal antibodies or steroids, cartilage degradation is minimized. The joint is further damaged by the release of lysosomal enzymes and bacterial toxins (Roy and Bhawan, 1975). Although some of these animal studies are preliminary, they emphasize the importance of the interaction of bacteria and host in the initiation and prolongation of infection and cartilage damage.

The virulence and tropism of the micro-organisms, combined with the resistance or susceptibility of the synovium to microbial invasion, are major determinants of joint infection. Staphylococcus aureus and Neisseria gonorrhoeae are examples of bacteria that have a high degree of selectivity for the synovium, probably related to their adherence characteristics and toxin production. Aerobic Gram-negative bacilli such as E. coli rarely infect the synovium, except in the presence of underlying conditions that result in the synovium being exceptionally susceptible to infection. The virulence of the organism once inside the joint varies with the organism. In rabbits, the intra-articular injection of $10^5$ S. aureus into the knee joint resulted in major joint destruction, but an identical injection of N. gonorrhoeae or S. epidermidis caused no joint inflammation (Goldenberg et al, 1983).
The infectious process induces a joint effusion that increases intra-articular pressure, mechanically impeding blood and nutrient supply to the joint. Thus increased pressure destroys the synovium and cartilage. Because of the proximity of the epiphyseal growth plate to the joint, direct extension of a joint infection to any of the articulating bones may lead to deceased bone growth in infants and children (Nelson and Koontz, 1966; Knights, 1982).

Risk factors

Certain medical conditions predispose joints to infection, degenerative joint disease, rheumatoid arthritis and corticosteroid therapy being the most common. Patients with diabetes mellitus, leukaemia, cirrhosis, granulomatous diseases, cancer, hypogammaglobulaemia or intravenous substance abuse, and those undergoing cytotoxic chemotherapy, also have an increased incidence of septic arthritis (Dickie, 1986; al-Eissa et al, 1990; Rozadilla et al, 1992). Total joint arthroplasties are susceptible to intra-operative or haematogenous seeding and subsequent prosthetic joint infection.

Gonococcal arthritis

Neisseria gonorrhoeae is the most common cause of septic arthritis in young healthy North American adults (Sharp et al, 1979; Knights, 1982; al-Eissa et al, 1990). The joint is infected by haematogenous spread of the organism from the primary mucosal site of infection. Females are four times as likely to become affected as males, and 50% of the females affected are either pregnant or menstruating at the time of the infection (O’Brian et al, 1983).

Gonococcal arthritis may present as part of a disseminated infection or as a monoarticular infection (Delauche et al, 1981). The presenting symptoms in disseminated gonococcal infection may include migratory arthralgias, fever, chills, dermatitis and tenosynovitis. Almost all of these patients have asymptomatic genital, anal or pharyngeal gonococcal infections. The classical skin lesion manifests as small erythematous papules that progress to vesicular or pustular lesions. There are typically 5–10 lesions around the affected joint. The tenosynovitis is characterized by pain, swelling and peri-articular erythema. Some patients develop septic gonococcal arthritis without prior polyarthritis or dermatitis. In the absence of the characteristic dermatitis or overt genital infection, septic gonococcal arthritis is clinically indistinguishable from other forms of septic arthritis (Silva and Wilson, 1979; Bayer, 1980).

Non-gonococcal bacterial arthritis

Non-gonococcal bacterial arthritis is an infectious process with serious sequelae. Mortality rates as high as 12% have been reported, and up to 75% of survivors develop a significant functional disability of the involved joint (Rosenthal et al, 1980). The classical presentation includes fever, pain, warmth, swelling and a decreased range of motion in the involved joint (Nelson and Koontz, 1966; Knights, 1982). Aspiration and culture of the joint effusion is critical in determination of the aetiological agent.

Which micro-organisms are responsible for bacterial arthritis depend largely on host factors, including age and risk factors such as intravenous drug abuse, asplenism, and joint infection following a domestic dog or cat bite. While the most
common aetiological agent for non-gonococcal bacterial arthritis in adults is *S. aureus*, Gram-negative bacilli account for approximately 20% of cases (Sharp et al, 1979; Dickie, 1986; Barton et al, 1987; Deesomchok and Timrasvin, 1990; Vyskocil et al, 1991). The most common Gram-negative organisms are *Pseud. aeruginosa* and *E. coli*. *Haemophilus influenzae*, group A Streptococci and *S. aureus*, listed in order of prevalence from highest to lowest, have been shown to be the most common causes of infectious arthritis in children under 3 years of age. However, the overall incidence of *H. influenzae* as a cause of septic arthritis is decreasing because of the *H. influenzae* vaccine now given to children (De Jonghe and Glaesener, 1995). A recent study of 165 cases of acute haematogenous osteomyelitis or septic arthritis treated in the years before and after the advent of the *H. influenzae* vaccine demonstrated that musculoskeletal infection due to this bacterial species was reduced to nearly non-existent levels (Bowerman et al, 1997). Therefore, with present vaccination strategies, the coverage of *H. influenzae* as part of the empirical antibiotic coverage may be no longer needed in the management of acute haematogenous osteomyelitis and septic arthritis in children. In children over the age of 3, *S. aureus* and *Strep. pyogenes* are usually isolated. Intravenous drug abusers have a significant rate of infection with Gram-negative organisms. While *S. aureus* is often isolated, *Streptococcus* spp. are responsible for 10–15% of cases (Goldenberg and Cohen, 1976; Vyskocil et al, 1991). Approximately 10% of patients with non-gonococcal septic arthritis have polymicrobial infections. Microbiological associations also exist with concomitant disease states. Septic arthritis following cases of infectious diarrhoea may be caused by *Shigella* spp., *Salmonella* spp., *Campylobacter* spp. or *Yersinia* spp. (Fryden et al, 1990; Keat, 1990). A rare form of migrating polyarthritis may be caused by *Streptobacillus moniliformis*.

**Diagnosis**

Septic arthritis is a medical emergency that can lead to significant morbidity and mortality. Therefore prompt recognition and treatment are critical in ensuring a good prognosis. Patients often present with a warm, tender and swollen joint with effusion and painful movements. However, the diagnosis of infectious arthritis rests on the isolation of the pathogen(s) from joint fluid obtained by aspiration or from debridement surgery (Bayer, 1980). Gram stains of the joint fluid may also provide a clue. Synovial fluid analysis is also very important and usually reveals turbid fluid with a leukocyte count in excess of 50 000/mm³. In bacterial arthritis, the fraction of polymorphonuclear leukocytes approaches 90% (Goldenberg and Reed, 1985; Shemerling et al, 1990). Peripheral blood leukocyte counts are usually elevated in children, but often lie within normal limits in adults. Radiographic studies may reveal joint space widening and soft tissue swelling in joints infected for longer than 2 weeks (Nelson and Koontz, 1966; Vyskocil et al, 1991).

**Treatment**

The treatment of septic arthritis includes appropriate antimicrobial therapy and joint drainage. The patient’s history and clinical course often provide clues for distinguishing between gonococcal and non-gonococcal arthritis. Initial antimicrobial therapy is based on the clinical presentation, initial Gram staining and joint fluid analysis. The initial antibiotic therapy is adjusted, if necessary, with reference to appropriate culture and sensitivity results.
Prognosis

The results of treatment vary greatly with the virulence of the invading organism, the adequacy of host defences, the integrity of the joint and the duration of symptoms prior to treatment. Patients who start treatment after 7 days of symptoms demonstrate a very poor outcome. The outcome in patients with septic arthritis arising from some of the more virulent organisms, for example superantigen-producing *S. aureus* and certain Gram-negative bacilli, is poor in spite of optimal therapy (Goldenberg and Cohen, 1976; Knights, 1982).

Early physical therapy and aggressive mobilization are important for optimal recovery (Sharp et al, 1979; Smith, 1990). Even with rapid and correct antibiotic treatment, the prognosis for good or excellent functioning of the joint is reported to range from 27% to 90%; while the mortality rate is reported as being 7–32% (Andersen et al, 1994).

SUMMARY

Infection occurs from a very large inoculation of organisms, trauma leading to bone damage, or the presence of foreign bodies. As the infection progresses, necrosis of normal tissue, new bone formation and local osteoporosis characterize osteomyelitis. While treatment may successfully arrest the infection, it must be understood that the bone infection may recur years later. Two methods that are currently used to classify osteomyelitis are the Cierny–Mader classification system and the Walldvogel classification system. According to the Walldvogel system, haematogenous osteomyelitis is usually found in paediatric patients in the long bone metaphyses and is usually caused by a single organism that reaches the bone through the blood system. In osteomyelitis secondary to a contiguous focus of infection, multiple organisms are usually isolated, and bacteria may be directly inoculated into the bone at the time of trauma, may extend from an adjacent infection such as a diabetic foot infection or may be spread by nosocomial contamination.

Bacterial arthritis is classed as either non-gonococcal or gonococcal. Virtually every bacterial organism has been reported to cause septic arthritis. Most septic joints are the result of haematogenous seeding, but they can also occur from bone infection extension and, rarely, joint aspiration or injection. *Neisseria gonorrhoeae* is the most common cause of septic arthritis in young healthy North Americans infected via haematogenous spread. The type of infecting bacterium in non-gonococcal arthritis is largely dependent upon host factors, including age and risk factors. While the most common infecting bacteria is *S. aureus*, Gram-negative bacilli account for approximately 20% of cases. Diagnosis depends upon isolation of the pathogen(s) from joint fluid. Treatment includes appropriate antimicrobial therapy and joint drainage. Treatment results vary greatly depending on the virulence of the invading organism, the adequacy of host defences, the integrity of the joint and the duration of symptoms prior to treatment.

Acknowledgements

The authors wish to thank Michael Cripps and Donna Milner Mader for manuscript review, reference research and preparation.
Practice points

Osteomyelitis
— Infection occurs from a very large inoculation of organisms, trauma leading to bone damage or the presence of foreign bodies.
— As the infection progresses, necrosis of normal tissue, new bone formation and local osteoporosis characterize osteomyelitis.
— While treatment may successfully arrest the infection, it must be understood that the bone infection may recur years later.

• Classification of osteomyelitis
  — Bone infections are currently classified by the Waldvogel as either haematogenous osteomyelitis or osteomyelitis secondary to a contiguous focus of infection (further subdivided into osteomyelitis with or without vascular insufficiency). An alternative classification system has been developed by Cierny and Mader, taking into consideration the quality of host, the anatomical nature of the disease and treatment and prognosis factors. This staging system combines four anatomical disease types and three physiological host categories to define 12 discrete clinical stages of osteomyelitis.

• Properties of osteomyelitis
  Haematogenous osteomyelitis in children
  — Haematogenous osteomyelitis is predominantly encountered in the paediatric population in the long bone metaphyses and is usually caused by a single organism.
  — *Staphylococcus* spp. are usually isolated.
  — Neonatal osteomyelitis is characterized by a lack of systemic and local findings but may present with local findings that include decreased motion of a limb and oedema.
  — Symptoms in the child include abrupt fever, irritability, lethargy and local signs of inflammation of 3 weeks or less in duration.
  — If antimicrobial therapy directed at the responsible pathogen is started prior to extensive bone necrosis, there is an excellent probability of arresting the infection.

Haematogenous osteomyelitis in adults
— Adults usually present with vague complaints consisting of non-specific pain and few constitutional symptoms of 1–3 months duration.
— The clinical signs resulting from soft tissue extension often dominate the findings at presentation and can lead to inappropriate diagnostic and therapeutic measures unless the clinical suspicion of an osseous aetiology is entertained.
— Vertebral osteomyelitis in the adult population is usually haematogenous in origin but may be secondary to trauma.
— A preceding history of urinary tract infection or intravenous drug abuse is often present.
— The disease usually involves two adjacent vertebrae and the intervening intervertebral disc.
— The lumbar vertebral bodies are most often involved, followed by the thoracic and cervical vertebrae.
the infection is usually monomicrobial (mostly *S. aureus*) when haematogenous in origin.

*Pseudomonas aeruginosa* and *Serratia marcescens* show a high incidence in intravenous drug users.

The patient usually presents with vague symptoms and signs consisting of dull, constant back pain and spasm of the paravertebral muscles.

Localized pain and tenderness of the involved bone segments is present in at least 90% of cases.

The pain is usually insidious and slowly progresses over the range 3 weeks to 3 months.

**Contiguous focus osteomyelitis**

In osteomyelitis secondary to a contiguous focus of infection, multiple organisms are usually isolated and bacteria may be directly inoculated into the bone at the time of trauma, may extend from an adjacent infection such as diabetic foot infection or may spread by nosocomial contamination.

*Staphylococcus aureus* and coagulase-negative Staphylococci account for 75% of the bacterial isolates, and Gram-negative bacilli and anaerobic organisms are frequently isolated.

Patients usually present with low-grade fever, pain and drainage.

The patients in this group range from 35 to 70 years of age.

The infection is commonly initiated by minor trauma of the feet, such as infected nail beds, cellulitis or trophic skin ulceration.

Osteomyelitis in vascularity compromised patients can be difficult to diagnose.

Examination shows decreased dorsal pedis and posterior tibia pulses, poor capillary refill and decreased sensation.

The treatment goal is to suppress the infection and maintain the functional integrity of the involved limb.

**Pathology of osteomyelitis**

Within the sequestra, the bacteria may be difficult to eradicate even after an intense host response, surgery and/or antibiotic therapy.

Clinically and histologically, acute osteomyelitis blends into chronic disease.

Because of lost blood supply, dead bone appears whiter than living bone.

New bone formation is also a characteristic feature of osteomyelitis.

Endosteal new bone may proliferate and obstruct the medullary canal.

After removal of the sequestrum, the remaining cavity may be filled with new bone, except in adults, where the cavity may persist or the space may be filled with fibrous tissue.

In time, it may be difficult to distinguish between the old living bone and the newly formed bone.

**Joint infections**

- **Source of infection**
  - Virtually every bacterial organism has been reported to cause septic arthritis.
—most septic joints develop as a result of haematogenous seeding of the vascular synovial membrane.

- **Pathogenesis**
  - while a normal inflammatory response is required in the host response to joint infection, significant destruction of the infected joint can occur when the inflammatory response is hyperactivated as a result of bacterial toxins.
  - *Staphylococcus aureus* and *N. gonorrhoeae* are examples of bacteria that have a high degree of selectivity for the synovium, probably related to adherence characteristics and toxin production.
  - Aerobic Gram-negative bacilli rarely infect the synovium.

- **Risk factors**
  - certain medical conditions predispose joints to infection.

- **Gonococcal arthritis**
  - *Neisseria gonorrhoeae* is the most common cause of septic arthritis in young, healthy North American adults.
  - Gonococcal arthritis may present as part of a disseminated infection or as a monoarticular infection.
  - Almost all of these patients have asymptomatic genital, anal or pharyngeal gonococcal infections.
  - There are typically 5–10 lesions around the affected joint.
  - Tenosynovitis is characterized by pain, swelling and peri-articular erythema.

- **Non-gonococcal bacterial arthritis**
  - Mortality rates as high as 12% have been reported, and up to 75% of survivors develop a significant functional disability of the involved joint.
  - Presentation usually includes fever, pain, warmth, swelling and a decreased range of motion in the involved joint.
  - Aspiration and culture of the joint effusion are critical in the determination of the aetiological agent.
  - The usual causes of this type of arthritis are *S. aureus* and *Strept. pyogenes*, but Gram-negative bacilli account for approximately 20% of cases.

- **Diagnosis**
  - Prompt recognition and treatment are critical in ensuring a good prognosis.
  - Patients often present with a warm, tender and swollen joint with effusion and painful movement.
  - The diagnosis of infectious arthritis rests on the isolation of the pathogen(s) from joint fluid obtained by aspiration or from debridement surgery.
  - Gram stains of the joint fluid may also provide clues.
  - Synovial fluid reveals turbid fluid with leukocyte counts in excess of 50 000/mm³, the fraction of polymorphonuclear leukocytes approaching 90%.
  - X-ray studies may reveal joint space widening and soft tissue swelling in joints infected for longer than 2 weeks.
• treatment
  — includes appropriate antimicrobial therapy and joint drainage.

• prognosis
  — patients who start treatment after 7 days of symptoms demonstrate a very poor outcome
  — the outcome in patients with septic arthritis caused by some of the more virulent organisms is poor in spite of optimal therapy
  — early physical therapy and aggressive mobilization are important for optimal recovery
  — in adults, this type of bone infection usually occurs in the lumbar and thoracic vertebrae.

---

**Research agenda**

**Osteomyelitis**

• cellular and molecular pathogenesis of osteomyelitis
  — further in vivo elucidation of those extracellular and cell-associated factors that contribute to the virulence of pathogenic organisms in osteomyelitis
  — possible prevention of osteomyelitis through vaccine development
  — the internalization and survival of S. aureus in osteoblasts and their in vivo relevance to immune system evasion, antimicrobial resistance and the chronic nature of infection
  — bone formation and resorption mediated by nitric oxide levels.

• classification of osteomyelitis
  — the utilization of different classification systems and their effect on treatment success
  — the relative importance of the various B host factors (according to the Cierny-Madersky staging system) and their effect upon the prognosis of patients with osteomyelitis.

• properties of osteomyelitis (based on the Waldvogel classification system)
  — the determination of whether osteomyelitis treatment failure is most often due to the specific host and bacterial properties, or due to the problems associated with the physician's technique and the choice of treatment modality
  — a retrospective study on the age-specific incidence of osteomyelitis caused by H. influenzae since the widespread use of the H. influenzae vaccine was instigated
  — determining whether the use of internal fixation in the treatment of traumatic bone injury is worth risking the possibility of the development of osteomyelitis
  — methods to reduce the chances of osteomyelitis developing in association with prosthetic implants, for example as a result of surgical techniques and different implant materials.
- easier and more effective treatment methods for contiguous focus osteomyelitis in patients without generalized vascular insufficiency
- the importance of neuropathy as a predictor of osteomyelitis in the diabetic patient
- determination of the efficacy of current diagnostic procedures for osteomyelitis in vascularly compromised patients
- the development of new procedures for the diagnosis of osteomyelitis in vascularly compromised patients that differentiate between soft tissue infection and osteomyelitis.

- pathology of osteomyelitis
  - the specific bacterial and host factors that enable an infection to become chronic, including but not limited to the glycocalyx, osteoblast invasion and the development of antimicrobial resistance in S. aureus
  - determination of the efficacy of new diagnostic procedures such as the quantitative polymerase chain reaction
  - the development and/or evaluation of new osteomyelitis treatment methods such as resorbable antibiotics or growth factor-impregnated beads to manage dead spaces following debridement surgery or including the role of growth factors.

Joint infections
- pathogenesis
  - analysis of bacterial isolates from joint cultures for toxins, these then being correlated with patient prognosis
  - better treatment regimens to reduce the morbidity and mortality associated with joint infection
  - new treatment that preferably reduces the level of immune system hyperactivation without interfering with the efficient clearance of bacteria from the host
  - determination of host factors and risk factors that increase the chances of contracting a joint infection and increase the morbidity and mortality associated with joint infection
  - a retrospective study on the age-specific incidence of joint infection resulting from H. influenzae since the widespread use of the H. influenzae vaccine was instigated
  - determination of the efficacy of current diagnostic procedures for joint infection and the development of new procedures for rapid and inexpensive diagnosis.

REFERENCES


