ABSTRACT: Osteomyelitis can affect every bone and is heterogeneous in its pathophysiology and presentation. When the diagnosis is clinically suspected, further studies such as serum inflammatory markers and imaging studies should be performed. Magnetic resonance imaging can be very useful in establishing the diagnosis and determining the extent of infection. When possible, bone specimens should be obtained and cultured prior to the initiation of antimicrobial therapy. Surgical debridement is often required for chronic or contiguous osteomyelitis for successful eradication of the infection. The ultimate test-of-cure is the lack of clinical relapse after the discontinuation of antimicrobials.

INTRODUCTION

Osteomyelitis is an infection of the bone and bone marrow. It can involve any bone of the human body and can occur through a variety of mechanisms. The difference in pathophysiology of various types of osteomyelitis mandates specific therapeutic strategies aimed at the eradication of the infection while preserving bone integrity and function. Osteomyelitis can be acute or chronic and may result from hematogenous seeding of the bone, extension of the infection from adjacent soft tissue, or direct inoculation of the bone through skin and soft tissue defects following trauma or surgery. Once established, osteomyelitis leads to progressive softening and necrosis of the bone resulting into the formation of sequestra. At this stage of the disease, surgical debridement becomes a requirement for cure. The presence of hardware at the site of infection is a complicating factor that could compromise treatment success. Despite adequate treatment, failure is not uncommon. Therefore, in order to improve the outcome, clinicians should understand the disease process and gain experience manipulating the treatment tools. Hence, the importance of this review.

MISE AU POINT/IN-DEPTH REVIEW

OSTEOMYELITIS: REVIEW OF PATHOPHYSIOLOGY, DIAGNOSTIC MODALITIES AND THERAPEUTIC OPTIONS

http://www.lebanesemedicaljournal.org/articles/60-1/review1.pdf

Albert J. EID, Elie F. BERBARI


ABSTRACT: Osteomyelitis can affect every bone and is heterogeneous in its pathophysiology and presentation. When the diagnosis is clinically suspected, further studies such as serum inflammatory markers and imaging studies should be performed. Magnetic resonance imaging can be very useful in establishing the diagnosis and determining the extent of infection. When possible, bone specimens should be obtained and cultured prior to the initiation of antimicrobial therapy. Surgical debridement is often required for chronic or contiguous osteomyelitis for successful eradication of the infection. The ultimate test-of-cure is the lack of clinical relapse after the discontinuation of antimicrobials.

INTRODUCTION

Osteomyelitis is an infection of the bone and bone marrow. It can involve any bone of the human body and can occur through a variety of mechanisms. The difference in pathophysiology of various types of osteomyelitis mandates specific therapeutic strategies aimed at the eradication of the infection while preserving bone integrity and function. Osteomyelitis can be acute or chronic and may result from hematogenous seeding of the bone, extension of the infection from adjacent soft tissue, or direct inoculation of the bone through skin and soft tissue defects following trauma or surgery. Once established, osteomyelitis leads to progressive softening and necrosis of the bone resulting into the formation of sequestra. At this stage of the disease, surgical debridement becomes a requirement for cure. The presence of hardware at the site of infection is a complicating factor that could compromise treatment success. Despite adequate treatment, failure is not uncommon. Therefore, in order to improve the outcome, clinicians should understand the disease process and gain experience manipulating the treatment tools. Hence, the importance of this review.

Herein, we will address the pathogenesis of osteomyelitis, the available diagnostic modalities, and various therapeutic strategies. Due to the difference in pathophysiology, microbiology, and management, we will separately discuss different entities including osteomyelitis due to open fractures, vertebral osteomyelitis, acute hematogenous osteomyelitis, osteomyelitis in patients with diabetes mellitus and osteomyelitis associated with prosthetic joint infection. A brief overview of osteomyelitis due to some specific pathogens such as *Brucella* species, *Salmonella* species, mycobacteria and fungi will also be reviewed.

PATHOGENESIS OF OSTEOMYELITIS

Experimental animal model of bone infection has revealed that bone is resistant to infection [1]. Osteomyelitis occurs only when a large inoculum of bacteria is introduced into the bone in conjunction with trauma, necrosis, or presence of foreign bodies [2]. Bacteria (i.e. *Staphylococcus aureus*) adhere to bone matrix via receptors to fibronectin, laminin, collagen and other structural proteins. Microorganisms elude the host defenses and antibiotics through a variety of mechanisms including surviving in a dormant state inside osteoblasts, developing a biofilm, and acquiring a very slow metabolic rate [3-4]. Furthermore, studies in a guinea pig model of post-traumatic osteomyelitis showed significant reduction of leukocyte locomotion after trauma and infection with *S. aureus* for up to 90 days [5]. The presence of prosthetic material contiguous to bone can lead to specific polymorphonuclear leu-
kocytes defect and therefore protects bacteria from phagocytosis. Inflammation, resulting from the interaction between bacteria and leukocytes, results in the release of cytokines and the development of osteolysis [3-4].

In patients with acute osteomyelitis of the long bones, it is believed that the metaphysis is the site of predilection due to slow blood flow in the metaphyseal vascular loops and the lack of phagocytic lining cells [6]. Once the infection is established in the metaphysis, the inflammatory exudate leads to increased pressure in the bone and intramedullary canal. Subsequently, the extension of this exudate into the cortex will eventually lead to periosteal elevation or rupture, disrupting the blood flow and causing bone infarction and the formation of an abscess or sequestrum. In chronic osteomyelitis, the inflammation is mild to moderate and little or no ischemic necrosis occurs [4].

The type and site of osteomyelitis is largely determined by the mechanism of infection, the virulence of the infecting organism, and the immune status and comorbid conditions of the patient [6-7] (Table I). Osteomyelitis could develop through hematogenous seeding of the bone from a remote source of infection, extension of the infection from adjacent soft tissue overlying the involved bone; or directly via inoculation of the bone following trauma or surgery.

**S. aureus** is the most commonly isolated organism in osteomyelitis. Other microorganisms such as coagulase-negative staphylococci, aerobic gram-negative bacilli, and anaerobes are frequently encountered as well (Table II). Patients with certain conditions such as immunosuppression, immune diseases (i.e. rheumatoid arthritis), diabetes mellitus, smoking, malnutrition, malignancy, extremes of age, chronic hypoxia, and renal or hepatic failure are at increased risk for osteomyelitis. Other local factors are equally important. Those include chronic edema, peripheral vascular disease, neuropathy, prior surgery, extensive scarring, and radiation fibrosis [6-8].

**DIAGNOSIS AND DIAGNOSTIC MODALITIES**

Osteomyelitis should be suspected when patients present with pain, swelling, erythema or warmth of the skin and soft tissue overlying bone. Subacute or chronic pain is commonly the only manifestation. Systemic symptoms (i.e. fever and chills) are present in patients with acute osteomyelitis but seldom present in patients with chronic osteomyelitis. Draining sinuses are typically seen in cases of chronic osteomyelitis. The presence of exposed bone or prosthetic material for a period of time is highly sug-

---

**TABLE I**

**ETIOLOGY OF OSTEOMYELITIS AND UNDERLYING CONDITIONS**

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Special groups</th>
<th>Etiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematogenous osteomyelitis</td>
<td>Common in children and adults</td>
<td><strong>Staphylococcus aureus</strong></td>
</tr>
<tr>
<td></td>
<td>Neonates</td>
<td>Enterobacteriaceae, Group B streptococci</td>
</tr>
<tr>
<td></td>
<td>Infants and children*</td>
<td><strong>Haemophilus influenzae group B</strong></td>
</tr>
<tr>
<td></td>
<td>Injection drug users</td>
<td><strong>Staphylococcus aureus, Pseudomonas aeruginosa, Candida spp.</strong></td>
</tr>
<tr>
<td>Vertebral osteomyelitis</td>
<td>Most common in adults</td>
<td><strong>Staphylococcus aureus</strong></td>
</tr>
<tr>
<td></td>
<td>Urinary tract infection</td>
<td>Aerobic gram-negative bacilli, <em>Enterococcus</em> spp.</td>
</tr>
<tr>
<td></td>
<td>Injection drug users</td>
<td><strong>Pseudomonas aeruginosa, Staphylococcus aureus, Candida spp.</strong></td>
</tr>
<tr>
<td></td>
<td>Following spine surgery</td>
<td>Coagulase-negative staphylococci, <em>Staphylococcus aureus</em>, aerobic gram-negative bacilli</td>
</tr>
<tr>
<td></td>
<td>Infections of intravascular devices</td>
<td>Candida spp.</td>
</tr>
<tr>
<td></td>
<td>In endemic regions</td>
<td>Mycobacterium tuberculosis, <em>Brucella</em> spp.</td>
</tr>
<tr>
<td>Contiguous focus osteomyelitis</td>
<td>Diabetes mellitus, vascular insufficiency, or following a contaminated open fracture</td>
<td>Polymicrobial: <em>Staphylococcus aureus</em>, beta-hemolytic streptococci, <em>Enterococcus</em> spp., aerobic gram-negative bacilli</td>
</tr>
<tr>
<td></td>
<td>Orthopedic fixation devices</td>
<td><strong>Staphylococcus aureus</strong>, coagulase-negative staphylococci</td>
</tr>
<tr>
<td></td>
<td>Cat bites</td>
<td><em>Pasteurella</em> multocida</td>
</tr>
<tr>
<td></td>
<td>Following puncture injuries on the foot by nails or other sharp objects</td>
<td><strong>Pseudomonas aeruginosa</strong></td>
</tr>
<tr>
<td></td>
<td>Following periodontal infection</td>
<td><em>Actinomyces</em> spp.</td>
</tr>
</tbody>
</table>

*The incidence of osteomyelitis due to Haemophilus influenza type B significantly decreased due to the routine vaccination of children.*
is isolated from those cultures
Aspergillus spp.
Mycoplasma spp.
in the operative specimen. However, less than
Mycobacterium avium
Tropheryma whipplei
Candida
Salmonella
Actinomycetes
osteomyelitis contained this organism [11]. Bone
white blood cell count is occasionally elevated. The
and C-reactive protein (CRP) are usually abnormal. The
a variety of laboratory, microbiologic, radiographic and
positive predictive value of 89% [9].

A.J. EID, E.F. BERBARI – Osteomyelitis
Lebanese Medical Journal 2012 • Volume 60 (1) 53
gestive of osteomyelitis. In fact, the probe-to-bone test is
widely used to diagnose osteomyelitis in patients with dia-
abetic foot ulcers and contiguous osteomyelitis. Grayson
et al. found that this test has a sensitivity of 66% and a
positive predictive value of 89% [9].

The confirmation of osteomyelitis requires the use of
a variety of laboratory, microbiologic, radiographic and
pathologic tests. Erythrocyte sedimentation rate (ESR)
and C-reactive protein (CRP) are usually abnormal. The
white blood cell count is occasionally elevated. The
platelet count can be elevated (inflammatory marker)
while the hemoglobin concentration can be low (anemia
of chronic disease). Blood cultures may be positive in
acute hematogenous and vertebral osteomyelitis. Cultures
of superficial wounds or sinus tracts should be cautiously
interpreted and should not be used to guide antimicrobial
therapy unless S. aureus is isolated from those cultures
[10-11]. In one study, only 44% of the sinus tract cultures
grew the same operative pathogen. The isolation of S. au-
reus from the sinus tract correlated with the presence of
S. aureus in the operative specimen. However, less than
half of the sinus tract cultures obtained from patients with
S. aureus osteomyelitis contained this organism [11]. Bone
tissue sampling via needle aspiration under radiologic
guidance or surgical procedure allow the identification of
the infectious organism and the determination of its in vitro
susceptibility profile [6]. The latter information is crucial
for the initiation of appropriate and effective antimicrobial
therapy (Table III). The bone tissue collected from the
infected site can also be submitted for histopathologic
examination which is considered the gold standard for the
diagnosis of osteomyelitis.

Conventional radiography has little value in diagnosing
acute osteomyelitis but it might be helpful in cases of
chronic osteomyelitis. At least 10-14 days are needed be-
fore abnormalities consistent with osteomyelitis are seen.
In one study, the sensitivity of plain radiographs in cases
of diabetic foot osteomyelitis was found to be 54%, while
the specificity was 68%. The radiographic signs that were
considered diagnostic included focal or geographic areas
of marrow lucency, loss of cortex with bony erosion, new
bone formation, bone sclerosis with or without erosion,
sequestration, involucrum, and periosteal elevation [12].

Nuclear bone scans using a variety of radiotracers (Technetium 99m methylene diphosphonate, Gallium-
citrate 67, and Indium 111-labeled white blood cells) are
commonly used to diagnose osteomyelitis. The perfor-
mance of those scans varies depending upon the clinical
situation [13]. In adults with normal radiographs (no
lesions that cause increased bone turnover), the three-
phase bone scan has higher accuracy than the other scans
with 94% sensitivity and 95% specificity. However, when
bone remodeling is increased, the specificity of the test
decreases to 33% [13]. In presence of osteomyelitis, sig-
nificant uptake is seen in all three phases of the study
(immediately after injection, at 15 minutes and 4 hours)
as opposed to increased uptake only in the first two phases
in patients with cellulitis. Gallium scans detect the areas
of inflammation due to the affinity of gallium-67 to acute
phase reactants (i.e. lactoferrin and transferrin) [14]. The
results of studies evaluating their sensitivity and specifici-
ity are not consistent. When studies are combined togeth-
er, the overall sensitivity is approximately 81% and the
specificity is 69% [13]. Some authors believe that gallium
scans have better performance for the evaluation of verteb-al osteomyelitis. This is supported by data from one
study showing high sensitivity, specificity and accuracy
[15]. Tagged white blood cell scans show accumulation of
tagged white cells in the bone marrow and at the site of
inflammation or infection [14]. In a meta-analysis, the sen-
sitivity of Indium 111-labeled white blood cells scan was
84% for extra-axial chronic osteomyelitis as opposed to
only 21% for the axial skeleton. Similarly, the specificity
was 80% in the peripheral skeleton and 60% in the axial
skeleton [16].

Positron emission tomography (PET) using 18-fluo-
rodeoxyglucose is increasingly being utilized in the diag-
nosis of osteomyelitis. In a systematic review and meta-
analysis, Termaat et al. found PET scans to have a sensi-
tivity of 96% and a specificity of 91% for the diagnosis of
osteomyelitis. [16]. PET scanning is a cheaper modality
when compared with other nuclear bone scanning tech-
niques and is typically performed in one day. Unfortu-
ately, however, false positive results can be seen with
bone healing. Computed tomography (CT) provides
excellent cortical bony details showing cortical bone ero-
sion or destruction and periosteal reaction. It could also
show small foci of air within the medullary canal, tiny for-
eign bodies serving as a nidus for infection and seque-
trum formation [17]. Magnetic resonance imaging (MRI)
is more sensitive than CT in detecting osteomyelitis and
as sensitive as nuclear studies. The sensitivity and speci-
cificity of MRI ranged from 82% to 100% and 75% to 96%,
respectively. MRI is considered the imaging modality of
choice in cases of established osteomyelitis because it
allows accurate determination of the extent of the infec-
tion, especially in case of vertebral osteomyelitis (iden-
tifies epidural abscess, phlegmon, and cord compression)
[17].

### TABLE II MICROBIOLOGY OF OSTEOMYELITIS

<table>
<thead>
<tr>
<th>Common</th>
<th>Less common</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococcus aureus</td>
<td>Mycobacterium tuberculosis</td>
</tr>
<tr>
<td>Coagulase-negative staphylococci</td>
<td>Rapidly growing mycobacteria</td>
</tr>
<tr>
<td>Streptococci</td>
<td>Mycobacterium avium complex</td>
</tr>
<tr>
<td>Enterococci</td>
<td>Endemic fungi</td>
</tr>
<tr>
<td>Pseudomonas spp.</td>
<td>Candida spp.</td>
</tr>
<tr>
<td>Enterobacter spp.</td>
<td>Aspergillus spp.</td>
</tr>
<tr>
<td>Proteus spp.</td>
<td>Mycoplasma spp.</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>Brucella spp.</td>
</tr>
<tr>
<td>Serratia spp.</td>
<td>Salmonella spp.</td>
</tr>
<tr>
<td>Anaerobes (Peptostreptococcus spp., Clostridium spp., B. fragilis group)</td>
<td>Actinomyces, Tropheryma whipplei</td>
</tr>
</tbody>
</table>
### TABLE III  
**ANTIMICROBIAL THERAPY FOR OSTEOMYELITIS DUE TO SPECIFIC MICROORGANISMS**

<table>
<thead>
<tr>
<th>Microorganisms</th>
<th>First choice</th>
<th>Alternative Choice</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Staphylococci, oxacillin-sensitive</strong></td>
<td>Naeglerin sodium or oxacillin sodium, 1.5-2.0 g IV q 4 hr for 4-6 wks OR</td>
<td>Vancomycin*, 20 mg/kg IV q 12 hr for 4-6 wks</td>
</tr>
<tr>
<td></td>
<td>Cefazolin 1-2 g IV q 8 hr for 4-6 wks</td>
<td></td>
</tr>
<tr>
<td><strong>Staphylococci, oxacillin-resistant</strong></td>
<td>Vancomycin*, 15 mg/kg IV q 12 hr for 4-6 wks</td>
<td>Linezolid 600 mg PO/IV q 12 hr for 6 wks</td>
</tr>
<tr>
<td><strong>Penicillin-sensitive streptococci</strong></td>
<td>Aqueous crystalline penicillin G, 20 x 10⁶ U/24 hr IV, either continuously or</td>
<td>Vancomycin*, 20 mg/kg IV q 12 hr for 4-6 wks</td>
</tr>
<tr>
<td></td>
<td>in 6 equally divided daily doses for 4-6 wks OR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ceftriaxone 1-2 g IV or IM q 24 hr for 4-6 wks OR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cefazolin 1-2 g IV every 8 hr for 4-6 wks OR</td>
<td></td>
</tr>
<tr>
<td><strong>Enterococci or streptococci</strong> with</td>
<td>Aqueous crystalline penicillin G, 20 x 10⁶ U/24 hr IV, either continuously or</td>
<td>Vancomycin*, 20 mg/kg IV q 12 hr for 4-6 wks</td>
</tr>
<tr>
<td>penicillin MIC ≥ 0.5 µg/mL or **</td>
<td>in 6 equally divided daily doses for 4-6 wks OR</td>
<td></td>
</tr>
<tr>
<td><em>Abiotrophia defectiva,</em> **</td>
<td>OR Amplicillin sodium 12 g24 hr IV either continuously or in 6 equally divided daily doses for 4-6 wks</td>
<td></td>
</tr>
<tr>
<td>Granulicatella spp., <em>Gemella spp.</em></td>
<td>Optional: Add Gentamicin sulfate, 1 mg/kg IV or IM every 8 hr for 1-2 wks</td>
<td></td>
</tr>
<tr>
<td><strong>Enterobacteriaceae</strong></td>
<td>Ceftriaxone 2 g IV q 24 hr for 4-6 wks</td>
<td>Ciprofloxacin** 500-750 mg PO q 24 hr for 4-6 wks</td>
</tr>
<tr>
<td><strong>Pseudomonas aeruginosa or</strong></td>
<td>Cefepime 2 g IV q 12 hr for 4-6 wks</td>
<td></td>
</tr>
<tr>
<td><strong>Enterobacter spp.</strong></td>
<td>Meropenem 1 g IV q 4 hr for 6 wks</td>
<td>Ciprofloxacin** 750 mg PO q 12 hr for 4-6 wks</td>
</tr>
<tr>
<td></td>
<td>OR Cefazidine 2 g IV q 8 hr for 4-6 wks</td>
<td></td>
</tr>
</tbody>
</table>

*IM: intramuscular  IV: intravenous  wks: weeks  PO: per os  *Dose based on normal creatinine clearance; vancomycin trough level should be 15-20.
**Should be avoided if possible, in the pediatric population and in osteomyelitis associated with fractures.

The optimal treatment of osteomyelitis is still not well defined due to the lack of prospective trials. Most of the data supporting treatment strategies derive from retrospective studies in humans. In expert opinions, current guidelines derive from studies in animal models, controlled clinical trials. The details of treatment will be discussed in the following sections addressing specific osteomyelitis entities.
quino
donal and gram-negative bacilli are less commonly isolated organism while coagulase-negative staphylococcal and gram-negative bacilli are less commonly encountered. Pseudomonas aeruginosa and Candida spp. are typically seen in intravenous drug users. Vertebral osteomyelitis due to Brucella spp. and Mycobacterium tuberculosis is common in endemic areas. When bacterial, fungal and mycobacterial stains and cultures. When the patient has concomitant bacteremia, it is safe to assume that his vertebral osteomyelitis is caused by the same organism isolated from the blood. Surgical debridement is necessary when patients present with an epidural abscess compressing the spinal cord, large paravertebral abscess, spine instability or failing medical treatment [6].

**Vertebral osteomyelitis and spondylodiskitis**

Vertebral osteomyelitis and intervertebral disk infection commonly result from hematogenous seeding via the segmental artery supplying two adjacent end plates of contiguous vertebrae [38]. Less frequently, vertebral osteomyelitis and disk space infection complicates spinal surgery. The routine use of preoperative antibiotic prophylaxis further reduced the incidence of postoperative spinal infection. In one study, the rates of infection with and without antimicrobial prophylaxis were 0.2% and 2.8%, respectively [39]. The infection involves most commonly the lumbar spine followed by the thoracic and cervical spine [40-41]. Vertebral osteomyelitis and disk space infection can be complicated with paravertebral and epidural abscesses. The latter could lead to spinal cord or nerve root compression and require urgent surgical intervention.

The majority of patients with vertebral osteomyelitis present with back pain while less than half have fever. Neurological symptoms such as motor or sensory deficits, bladder and bowel incontinence are not uncommon and should receive urgent attention. *S. aureus* is the most commonly isolated organism while coagulase-negative staphylococcal and gram-negative bacilli are less commonly encountered. Pseudomonas aeruginosa and Candida spp. are typically seen in intravenous drug users. Vertebral osteomyelitis due to Brucella spp. and Mycobacterium tuberculosis is common in endemic areas. When bacteremia is present, endocarditis should be ruled out [41-43].

Spine MRI is the test of choice when vertebral osteomyelitis is suspected. Gallium or PET scans are alternatives when MRI cannot be performed (i.e. patients with claustrophobia or patients with implantable cardiovascular devices). If the diagnosis is supported by imaging studies, a microbiological diagnosis should be established. CT-guided percutaneous biopsies are easy to perform but have limited sensitivity (52%) [44]. When the results of the first percutaneous biopsy are inconclusive, a second CT-guided biopsy should be attempted before resorting to an open biopsy. Tissue should be submitted for pathology as well as bacterial, fungal and mycobacterial stains and cultures. When the patient has concomitant bacteremia, it is safe to assume that his vertebral osteomyelitis is caused by the same organism isolated from the blood. Surgical debridement is necessary when patients present with an epidural abscess compressing the spinal cord, large paravertebral abscess, spine instability or failing medical treatment [6].

Effective antimicrobial therapy should be given for at least four to six weeks. When vertebral osteomyelitis is treated with surgical debridement and instrumented spine...
fusion or when hardware-associated osteomyelitis develops following spinal surgery, some experts recommend parenteral antibiotic therapy followed by oral suppressive antibiotic therapy for up to two years to allow bone healing [6].

**Acute hematogenous osteomyelitis**

Acute hematogenous osteomyelitis occurs mainly in prepubertal children. Long tubular bones (i.e. femur, tibia, and fibula) are more commonly affected than flat bones and spine [45]. Multiple bones could be infected concomitantly. The infection originates in the metaphyseal region and can extend to the cortex or the epiphysis and joint space. *S. aureus* and *Streptococcus pneumoniae* are responsible for most cases. Children present with pain in the metaphyseal region of a long bone. Blood cultures are typically positive. Radiological findings such as periosteal new bone formation (periosteal elevation) or bone destruction support the diagnosis. If plain radiographs are not conclusive, MRI may establish the diagnosis. Blood cultures should be obtained before administering antimicrobials. Bone, subperiosteal exudate, and synovial fluid should be obtained if possible in order to identify the infecting microorganism. Acute hematogenous osteomyelitis in children is frequently treated with antimicrobial therapy alone. Antibiotics are typically given for three weeks. Sequential therapy with intravenous followed by oral antibiotics is commonly used. Surgical treatment is considered in case of no clinical response after 48 hours of antibiotic therapy, septic arthritis, or failure to cure the infection despite adequate antibiotic therapy. Adequate and prompt treatment leads to excellent outcome in newborns, infants and children; however, in cases associated with septic arthritis or complicated with the destruction of the growth plate, the prognosis is more reserved. In those situations, abnormal growth of the affected bone is likely to occur and significant damage of the infected joint might be irreversible [46].

**Osteomyelitis in patients with diabetes mellitus**

Patients with diabetes mellitus are at increased risk of developing foot infections due to hyperglycemia, neuropathy, and peripheral vascular disease. During their lifetime, 15% of diabetic patients develop foot ulcers and 6% are hospitalized because of those ulcers [47].

The infectious process usually originates at the site of an ulcer and commonly progresses to reach contiguous bone. When the size of an ulcer is > 2 x 2 cm and when ESR is > 70 mm/hour, osteomyelitis is more likely to be present [48]. The presence of exposed bone or the ability to probe the bone is strongly suggestive of underlying osteomyelitis (positive predictive value of 89%) [9, 48-49]. Further testing is not required when the probe-to-bone test is positive. In other situations, plain radiographs, nuclear bone scans, or MRI could be helpful to establish the diagnosis. ESR and CRP should always be measured at baseline and monitored during therapy to assess response.

Chronic osteomyelitis in patients with diabetes mellitus is usually polymicrobial. Multiple aerobic and anaerobic bacteria can be involved. When possible, bone tissue should be submitted for cultures prior to the initiation of antimicrobial therapy. When hemodynamically significant stenosis is present, revascularization should be considered before surgical debridement of the infected foot. Intravenous antimicrobials such as piperacillin-tazobactam, ticarcillin-clavulanate, ampicillin-sulbactam, Erta penem, or other β-lactams in combination with metronidazole are commonly used. An oral regimen consisting of levofloxacin or moxifloxacin with metronidazole or clindamycin can also be used [50]. HBOT might be beneficial in this context due to limited oxygenation of the infected tissue and the likelihood of anaerobic infection; however, data from randomized, controlled studies are lacking. Limited amputation of the limb should be considered in cases with persistent or recurrent osteomyelitis despite optimal therapy.

**Osteomyelitis associated with prosthetic joint infection**

Joint arthroplasty represent a true success story due to its ability to restore function. The projected number of patients who will undergo arthroplasty in the United States in 2030 is 3-4 millions [51]. It is estimated that 0.8 to 1.9% of knee arthroplasties and 0.3 to 1.7% of hip arthroplasties get infected [52]. The treatment also consists of a combination of surgical and antimicrobial therapy. Three different therapeutic strategies are available:

1. Surgical debridement and retention of the prosthesis is an option when certain criteria are met. Those include duration of symptoms < 3 weeks, infection developing within 3 months of arthroplasty or presentation consistent with hematogenous seeding, well-fixed prosthesis, adequate soft tissue envelop, absence of sinus tract, and established microbiologic diagnosis and favorable susceptibility profile [52-53].

2. One-stage exchange entails resection of the infected prosthesis, debridement of the infected tissue and immediate implantation of a new prosthesis. Antibiotic-impregnated PMMA cement is frequently used during reimplantation. This strategy is not advisable when the infection is caused by virulent organisms (i.e. *S. aureus*, Gram-negative bacteria) or in presence of draining sinus or significant purulence.

3. Two-stage exchange consists of resection of the infected prosthesis, debridement of the infected tissue and immediate implantation of a new prosthesis 2-6 weeks after finishing antimicrobial therapy. The use of a spacer impregnated with antimicrobial(s) (i.e. vancomycin, gentamicin or tobramycin) is a common practice currently and was shown to reduce the rate of recurrent infection [54]. Antimicrobial therapy should be guided by *in vitro* susceptibilities (Table III). Following debridement and retention of the prosthesis, Rifampin was successfully used in combination with fluoroquinolones. The duration of treatment was 3-6 months for prosthetic knee infection and 6 months for prosthetic hip infection [27, 55]. Shorter
course (4 weeks) of parenteral antibiotic therapy can be given followed by suppressive oral antibiotic therapy [56]. Rifampin-based regimen is also recommended after one-stage exchange.

Osteomyelitis in injection drug users

Intravenous drug use is associated with hematogenous osteomyelitis due to the introduction of bacteria and fungi into the bloodstream. However, direct inoculation or contiguous spread is also possible [6]. Multifocal infections may occur. The spine, sterno-clavicular, sterno-chondral, and sacro-iliac joints are commonly involved [57-58]. The most common organisms responsible for osteomyelitis in injection drug users (IDU) are *S. aureus*, *Pseudomonas* species, and *Candida* species. *Eikenella corrodens*, which is part of the normal oral flora, is seen in IDU who lick their needles or skin prior to injection (“needle licker’s osteomyelitis”) [59]. *M. tuberculosis* can cause skeletal infection in IDU and most cases involve the spine [60]. Treatment of osteomyelitis in IDU is similar to treatment of other patients; however, an oral regimen should be used, if at all possible, to avoid using long-term intravenous access (e.g. peripherally inserted intravenous catheter).

Osteomyelitis due to Brucella species

Brucellosis is endemic in the Mediterranean basin and the Arabian Gulf; therefore, osteomyelitis due to *Brucella* species should be considered in this setting. Brucellosis is commonly transmitted via ingestion of contaminated food such as raw milk, cheese made from unpasteurized milk, or raw meat. Infection could also result from direct skin inoculation through skin abrasions or cuts during contact with animal carcasses, placentas, and animal vaginal secretions. Patients present with fever, night sweats, arthralgias, anorexia and fatigue. When the diagnosis is delayed, localized infection occurs. Osteoarticular infections, mainly sacroiliitis, represent 20-30% of those localized infections [61-62]. Specific cultures (Ruiz-Castaneda or lysis centrifugation) or prolonged incubation of cultures can be used to establish a diagnosis. Serological studies using serum agglutination (standard tube agglutination) and enzyme-linked immunosorbent assay (ELISA) can be very helpful, especially in case of negative cultures. The combination of doxycycline-streptomycin or doxycycline-streptomycin-rifampin seem to be more effective than doxycycline-rifampin [63-64]. Ciprofloxacin-rifampin can be considered as an alternative regimen for doxycycline-streptomycin when patients experience drug toxicity [65]. Osteoarticular disease, similar to other localizing manifestations, carries with it higher risk of relapse compared to brucellosis without localizing disease. Therefore, antibiotic therapy should be administered for 3-6 months [61, 64] in order to minimize the risk of relapse.

Osteomyelitis due to Salmonella species

Osteomyelitis due to *Salmonella* species is uncommon accounting for 0.45% of all osteomyelitis cases and is seen in only 0.8% of all *Salmonella* infections [66]. Patients with sickle cell disease, however, have much higher risk of developing this infection. Other risk factors include comorbidities such as diabetes mellitus, systemic lupus erythematosus, lymphoma, liver disease, previous surgery or trauma, treatment with steroids, and extremes of age [66]. Patients are usually treated with third-generation cephalosporins or fluoroquinolones. In anecdotal reports, the duration of successful antibiotic therapy ranged from 6-12 weeks [66-69].

Osteomyelitis due to mycobacteria

Osteomyelitis can result from infection due to *M. tuberculosis* or non-tuberculous mycobacteria (NTBM). Mycobacterial osteomyelitis should be suspected when bacterial cultures remain negative or when granulomatous inflammation is identified in bone tissue [70]. Tuberculosis (TB) of the musculoskeletal system represents 1-5% of all TB cases [6]. Osteomyelitis is attributed to hematogenous seeding of the bone at the time of primary infection and should be considered in patients with history of treated or untreated tuberculosis, known exposure to *M. tuberculosis*, positive tuberculin skin test, and evidence of old or active TB on chest X-ray. Pott’s disease or vertebral osteomyelitis due to *M. tuberculosis* represents around 50% of all musculoskeletal TB cases [71]. The lumbar and lower thoracic spine is more commonly involved than the upper thoracic and cervical spine [72-73]. In 50% of cases, spine MRI shows evidence of paravertebral abscesses and those are frequently bilateral. Extraspinous tuberculosis presents with swelling, pain, and mild erythema. A “cold abscess” is usually present and spontaneous drainage through a sinus tract could occur. The most common manifestations of spinal osteomyelitis are pain and stiffness. Due to delayed diagnosis, neurological deficit due to spinal cord compression is present in 42-76% of patients [74-75]. Treatment of tuberculous osteomyelitis is for the most part medical. The regimens of antituberculous medications used to treat osteoarticular TB are similar to those used to treat other forms of TB, but treatment should be given for a longer period of time (12-18 months) [76]. Surgical therapy might be necessary for abscess drainage, cord decompression, and spinal stabilization [74].

Musculoskeletal infections due to NTBM seem to have increased in frequency over the past few years, possibly due to better recognition of this infection [77]. Multiple species can be responsible for osteomyelitis and those include *M. abscessus*, *M. chelonae*, *M. fortuitum*, *M. marinum*, *M. avium-intracellulare*, *M. kansasi*, *M. xenopi* and *M. terrae* complex [78-81]. The infection develops in bones, joints, bursae, or tendon sheaths following direct inoculation at the time of surgery, trauma, puncture wounds, or injections (intraarticular or extraarticular). Patients present with non-healing wounds associated with chronic drainage and sinus formation. Axial bone or extremities could also be infected through hematogenous seeding. Mycobacterial cultures of tissue specimens are required to establish a diagnosis; however, rapidly-grow-
ing mycobacteria grow on routine cultures as well. The identification of the infecting species and its susceptibility profile are crucial to guide antimicrobial therapy. A combination of two or three antibiotics (depending upon the degree of severity of the infection) should be used to treat the infection. The antibiotics should be determined based on the susceptibility profile. Osteomyelitis due to rapidly-growing mycobacteria is treated for six months while osteomyelitis due to other mycobacteria is treated for at least 12 months [82].

Osteomyelitis due to fungi
Fungal osteomyelitis is more likely to result from disseminated fungal infection than direct inoculation of the bone. Osteomyelitis is commonly seen with disseminated endemic fungal infections such as blastomycosis, coccidioidomycosis and sporotrichosis. Up to 25% of patients with disseminated blastomycosis develop osteomyelitis [83]. Candida osteomyelitis can complicate candidemia or result from surgical site infection. Even though uncommon, disseminated Aspergillus and Cryptococcus infections in immunocompromised patients can lead to osteomyelitis. Fungal osteomyelitis due to molds such as Pseudallescheria boydii, Scedosporium prolificans, and Fusarium species is usually seen with open contaminated fractures. The clinical context is often helpful to identify the fungus responsible for osteomyelitis. The role of surgical treatment is relatively limited and the medical treatment depends on the etiology.

Recurrent osteomyelitis
Patients presenting with recurrent osteomyelitis should undergo comprehensive evaluation in order to determine the underlying etiology. Recurrence of osteomyelitis could be attributed to a variety of factors. Those include incorrect microbiological diagnosis, inability to culture the true pathogen (e.g. Mycobacteria, Coxiella, Mycoplasma, and Chlamydia species), use of inappropriate or suboptimal dose of antimicrobial(s), development of resistance of the infecting organism, and inadequate surgical debridement of the infected bone. Occasionally, failure of treatment is attributed solely to the virulence of the infecting bacteria (e.g. Brucella species, MRSA). Antibiopic therapy should be held for at least two weeks prior to repeat surgical debridement. Tissue specimens must be submitted for aerobic and anaerobic bacterial, as well as fungal and mycobacterial cultures. Following surgery, antimicrobial therapy should be guided by culture results and in vitro susceptibilities.

CONCLUSION
Osteomyelitis continues to be a serious infection associated with high relapse rate and significant morbidity and loss of function. Preventive strategies should be emphasized and widely implemented in order to reduce the incidence, especially in high risk patients such as those with diabetes mellitus. When osteomyelitis develops, the patient should be treated by a multidisciplinary team including an orthopedic surgeon, vascular surgeon, plastic surgeon, interventional radiologist, endocrinologist and an infectious diseases specialist. Such an approach provides the best chance for cure and restoration of function.

REFERENCES
16. Termaat MF, Rajimakers PG, Scholten HJ, Bakker FC, Patka P, Haarman HJ. The accuracy of diagnostic imaging for the assessment of chronic osteomyelitis : a-s