Diagnosis and management of osteomyelitis

Gunawan,1 B Setiyohadi2

ABSTRACT
Osteomyelitis is an infection of the bone that causes bone destruction and formation of new bone as the result of the inflammatory process. Proper diagnosis in osteomyelitis is important since it determines the decision-making in the management of the disease: whether to perform aggressive treatments or administration of long-term antibiotic treatment. Imaging techniques play an important role in the diagnosis of osteomyelitis, but their results should be interpreted with care as they have a wide range of sensitivity and specificity. A combination of imaging techniques could improve their sensitivity and specificity. Conventional radiography is an affordable and widely available technique, and has been proven to be useful in diagnosing and excluding the differential diagnoses of osteomyelitis. Surgical intervention to remove necrotic tissues and administration of antibiotics to eradicate pathogens are necessary in the management of osteomyelitis. Several antibiotics such as quinolones, rifampin, and clindamycin have been proven to have good penetration into bone.

Osteomyelitis is an infection of the bone that causes bone destruction and formation of new bone as the result of the inflammatory process. The first report about osteomyelitis was written circa 400 BC by Hippocrates, who described it as “a boil of the bone marrow”. Terms such as “abcessus in medulla” or “necrosis” were also used to describe the condition until Nelaton introduced the term “osteomyelitis” in 1844. In the last 40 years there has been much development in the definition, pathogenesis, diagnosis, and treatment of osteomyelitis.1,2 Osteomyelitis management has always been a challenge. Before the use of antibiotics in the 1940s, the treatment of choice for osteomyelitis was surgical therapy, with wide incision to remove all of the necrotic bone. This procedure had a high mortality rate, which could reach 33%. After the discovery of more potent antibiotics, complications of osteomyelitis such as sinus formation, sequestration, and sepsis are now rarely encountered. Besides, the aim of therapy has also changed from merely palliative to curative.2

New diagnostic techniques, aggressive surgical methods with the use of prostheses, and the availability of safe broad spectrum antibiotics help the management of osteomyelitis in outpatient settings. However, the increasing number of immunocompromised patients (particularly those with human immunodeficiency virus/acquired immunodeficiency syndrome or receiving immnosuppressive treatment) adds to the prevalence of osteomyelitis and antibiotic resistance, which present major challenges in the management of osteomyelitis.

DEFINITION
Osteomyelitis is defined as infection affecting bones, causing destruction and formation of new bone. There are several mechanisms of infection that may cause osteomyelitis: (a) contiguous focus of infection (eg. after trauma, surgery, or insertion of prosthetic joint); (b) vascular insufficiency (eg. in diabetes mellitus or peripheral vascular disorder); and (c) hematogenous spread of infection (eg. in vertebral osteomyelitis in children). Based on the duration of disease, osteomyelitis is divided into acute and chronic osteomyelitis (Lee and Waldgovel classification).3,4 Acute osteomyelitis will usually resolve in several days to weeks, although it may also progress to chronic osteomyelitis. There is no precise definition for when osteomyelitis becomes chronic but it is defined as such if the infection persists for weeks or years.2

PATHOGENESIS
Normally, bone tissue is resistant to infection. Osteomyelitis occurs when there is inoculation of a large number of microorganisms, preceeding trauma, or presence of foreign material in the bone. The pathogenesis of osteomyelitis is multifactorial and has yet to be fully understood. Some important factors in the pathogenesis are pathogenic virulence; coexisting disease and host immunity; and bone type, location, and vascularization.

The pathogenic determinants of osteomyelitis are bacterial adherence, activity of proteolytic enzymes produced by the pathogen, and resistance to host immunity. Bacterial adherence plays a role in osteomyelitis and arthritis caused by Staphylococcus aureus. This bacteria has the ability to adhere to some bone matrix components, such as fibrinogen, fibronectin, laminin, collagen, sialoglycoprotein, and factor A.5–9 The adherence process is mediated by specific adhesin expressed by S. aureus, called microbial surface components recognizing adhesive matrix molecules (MSCRAMM).5–10 Proteolytic activity can be found under normal conditions in a joint without inflammation. In the
presence of infection, the inhibition of proteolytic activity is diminished. In an in vitro study by Williams et al that inoculated *S. aureus* into mature chondrocytes, there was a decrease in protein matrix synthesis and release of collagenases and gelatinases.11

Resistance to host immune responses at the cellular level as well as in the extracellular matrix also complicates the management of osteomyelitis. *S. aureus* has been found to be present inside the cultured osteoblasts. Production of arachidonic acid metabolites such as prostaglandin E2, which is a potent agonist of osteoclasts, reduces the number of bacteria needed for the infection to occur. Protein A expressed by *S. aureus* on the cell wall peptidoglycan binds with Fc components of polymorphonuclear cells and thus disrupts the opsonization and phagocytosis against *S. aureus*. Furthermore, secretion of exotoxin and toxic shock syndrome toxin-1 (TSST-1) suppresses plasma cell differentiation and causes an increase in cytokine production such as interleukin-1, interferon γ (IFNγ), and tumor necrosis factor α (TNFα).15,16

**PATHOPHYSIOLOGY**

As stated above, osteomyelitis could be caused by direct pathogen inoculation following trauma of surgery, contiguous spread from adjacent soft tissue or joint, or hematogenous spread from a focus of infection. Hematogenous osteomyelitis is usually monomicrobial, while the other types are polymicrobial.

In the long bones, osteomyelitis usually affects the metaphyseal area since the main vascularization enters the bone in its middle part, runs on both sides of the bone through its length, and forms loops before reaching the epiphyseal plate. The decrease in blood flow and the absence of basal membrane in the metaphysis predispose this area to infection.

In the presence of infection, inflammatory exudates cause increases in intramedullary pressure and extension of the exudates into the cortex, with subsequent rupture through the periosteum. These will disrupt the blood supply to the periosteum and cause necrosis of the bone, with fragments of necrotic bone (sequestra) detectable on radiographs. There is also formation of new bone ( involucrum) around the damaged periosteum.

In acute osteomyelitis, infection occurs before the development of sequestra. In some forms of infection, development of sequestra is relatively slow (such as vertebral osteomyelitis), while in others the development of sequestra occurs relatively rapidly (such as osteomyelitis in the setting of prosthetic devices). In vertebral osteomyelitis, infection may involve two adjacent vertebrae simultaneously, since their vascularization is supplied by a single artery.

**CLASSIFICATION**

There are two classification systems commonly used in osteomyelitis: Lee-Waldvogel and Cierny-Mader classification.1,4

Lee and Waldvogel classified osteomyelitis according to the duration of disease (acute vs. chronic) and the mechanism of infection (hematogenous vs. secondary to contiguous focus of infection). This classification is based on etiology and is not used for choosing specific treatments.

Cierny and Mader classified osteomyelitis based on the part of the bone involved, host physiological status, and local environment (table 1). This system could be used as a guidance for the management of osteomyelitis: stage 1 can be sufficiently treated with antibiotics, while stages 2 to 4 usually require more aggressive treatment such as debridement or orthopedic reconstruction, if necessary.

**Table 1** Cierny and Mader classification of osteomyelitis

<table>
<thead>
<tr>
<th>Anatomic type</th>
<th>Description</th>
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<tbody>
<tr>
<td>Stage 1: Medullary osteomyelitis</td>
<td>Infection only involves intramedullary surface of bone, e.g. in hematogenous infection and bone marrow infection.</td>
</tr>
<tr>
<td>Stage 2: Superficial osteomyelitis</td>
<td>True osteomyelitis, caused by direct inoculation or contiguous focus of infection after exposure of necrotic bone surface under damaged soft tissue.</td>
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<tr>
<td>Stage 3: Localized osteomyelitis</td>
<td>Marked by presence of thick sequestra on bone cortex; this could be removed surgically without disturbing bone stability.</td>
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<tr>
<td>Stage 4: Diffuse osteomyelitis</td>
<td>At this stage, bone resection is usually required to stop the infection; bone may lose its stability before or after the debridement.</td>
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**DIAGNOSIS**

Symptoms of acute osteomyelitis usually develop over several days. Patients will complain of dull pain in the involved bone, accompanied with local symptoms such as tenderness, redness, swelling, warmth, and systemic symptoms such as fever, shivering, and malaise. In some cases affecting hip, vertebrae, or pelvis, pain may be the only symptom. Acute osteomyelitis may also coexist with septic arthritis, because infection from metaphysis could extend to joint following cortex destruction caused by intramedullary inflammation. Clinical manifestations of chronic osteomyelitis are pain, erythema, edema, and occasionally formation of cutaneous sinus; the latter is pathognomonic for osteomyelitis.

Diagnosis of osteomyelitis may be more difficult in the presence of prosthesis, extensive ulcer, or vascular insufficiency.17 In general, osteomyelitis should be taken into consideration when there is persistent wound or ulcer on the skin despite adequate treatments. Diabetic patients who have ulcer and chronic osteomyelitis may give noncharacteristic clinical feature, e.g. osteomyelitis may occur before the
exposure of underlying bone through the skin ulcer. In that case, the possibility of osteomyelitis is even greater if the bone is clearly exposed. In the presence of ulcer larger than 2 × 2 cm, or if the underlying bone is palpable, diagnosis of osteomyelitis is so likely that further noninvasive evaluation is unnecessary.17,18

Proper diagnosis in osteomyelitis is important because it determines the decision-making in the management of the disease: whether to perform aggressive treatments or administration of long-term antibiotic treatment. The diagnostic standards for osteomyelitis are isolation of pathogens from bone biopsy and histopathologic presence of inflammation and osteonecrosis.19

Diagnostic tests, particularly imaging techniques, play important roles in diagnosing osteomyelitis. However, results of diagnostic imaging procedures should be interpreted with care as they have a wide range of sensitivity and specificity. Conventional radiography is both affordable and widely available, and has been proven to be useful in diagnosing and excluding the differential diagnoses of osteomyelitis. Imaging findings in chronic osteomyelitis include cortical erosion, periosteal reaction, and mixed lucency and sclerosis.19,20

Figure 1 shows an example of imaging result of chronic osteomyelitis.

**Figure 1** (A) Sagittal fluid-sensitive short-tau inversion recovery (STIR) image demonstrates high signal fluid collection along the plantar surface of the calcaneous (white arrow); (B) Sagittal postcontrast T1-weighted image with fat saturation demonstrates the peripherally enhancing fluid collection (white arrow); (C) Sagittal T1-weighted precontrast image demonstrates some cortical interruption (white arrow); (D) Lateral radiograph demonstrates soft tissue loss overlying the plantar aspect of the calcaneous (white arrow). Osseous remodeling and periosteal reaction about the posterior calcaneous (asterisk) reflect changes associated with longstanding chronic osteomyelitis. (Adapted from Horwich, 2010)21

In a meta-analysis22 of studies comparing imaging techniques with histological analysis, findings on culture, and clinical follow-up of more than six months, conventional radiography has sensitivity and specificity of 54% and 68%, respectively. To improve sensitivity, conventional radiography can be combined with other imaging techniques. Bone scintigraphy has better sensitivity (81%) but limited specificity (28%). In contrast, leukocyte scintigraphy has better specificity (68%) although it has lower (74%) sensitivity compared with bone scintigraphy. Combination of bone and leukocyte scintigraphy could improve their sensitivity and specificity. The comparison of sensitivity and specificity of several imaging techniques are shown in table 2.

**Table 2** Sensitivity and specificity of several imaging techniques in osteomyelitis22

<table>
<thead>
<tr>
<th>Imaging technique</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
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<tbody>
<tr>
<td>Probe to bone/exposed</td>
<td>0.60 (0.46–0.73)</td>
<td>0.91 (0.86–0.94)</td>
</tr>
<tr>
<td>Conventional radiography</td>
<td>0.54 (0.44–0.63)</td>
<td>0.68 (0.53–0.80)</td>
</tr>
<tr>
<td>MRI</td>
<td>0.90 (0.82–0.95)</td>
<td>0.79 (0.62–0.91)</td>
</tr>
<tr>
<td>Bone scintigraphy</td>
<td>0.81 (0.73–0.87)</td>
<td>0.28 (0.17–0.42)</td>
</tr>
<tr>
<td>Leukocyte scintigraphy</td>
<td>0.74 (0.67–0.80)</td>
<td>0.68 (0.57–0.78)</td>
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</table>

Computed tomography (CT) scan and magnetic resonance imaging (MRI) are the more popular techniques in the diagnosis of osteomyelitis. To date, MRI is the best technique to acquire anatomical images of bone marrow involvement and inflammation. MRI is also reliable in diagnosing pedal (in diabetic patients) and vertebral osteomyelitis (detailed visualization of spinal nerves and neighboring structures).23,24 Gadolinium contrast is used to obtain better visualization of sinuses, fistulas, and abscesses. MRI has a high negative predictive value; therefore the possibility of osteomyelitis can be excluded if the symptoms have been present for 1 week. Edema visualized in MRI is not specific for infection: contusion, fractures, or history of surgery may yield similar findings; thus interpretation of bone marrow edema on MRI should be guided by clinical findings and other diagnostic tests.25,26 CT scan is the technique of choice when MRI could not be performed. It is useful in evaluating cortical and trabecular integrity, periosteal reaction, intraosseous gas, and the extent of sinus tracts.27–29

One of the drawbacks of imaging techniques is their limited ability to differentiate osteomyelitis from noninfectious lesions, such as trauma, surgery, recently healed osteomyelitis, septic arthritis, degenerative joint diseases, bone tumors, Paget’s disease, and other noninflammatory bone diseases.30,31

Currently there is no specific laboratory test for diagnosing osteomyelitis. There may be leukocytosis, particularly in the acute phase of infection, and increase in erythrocyte sedimentation rate (ESR) and/or C-reactive protein (CRP).32,33 Blood culture is positive in 50% cases and is more common in cases with hematogenous spread.

**MANAGEMENT**

In the management of osteomyelitis, both surgical intervention to remove necrotic tissues and administration of antibiotics to eradicate pathogens are necessary. Antibiotic treatment should be given in accordance with culture and sensitivity results. If culture results have not arrived, empirical antibiotic treatment should be started immediately. Some recent antibiotic regimens
for the management of osteomyelitis are shown in table 3. Osteomyelitis caused by Gram-negative microorganisms is best treated with quinolones (after confirmation by sensitivity test) because their good penetration into bone, even with oral administration. Several in vitro studies showed that rifampin, clindamycin, and quinolones also penetrate well into bone. Use of prostheses may increase antibiotic resistance by formation of biofilms. Some experts suggest combination of rifampin with other antibiotics since there is high rates of resistance when it is used alone.

Antibiotics is usually given in long-term because there is persistence of *S. aureus* in osteoelasts, as has been showed by several animal studies. In some patients, penetration of antibiotics can be disrupted if there is vascular disorder or post-traumatic scar tissue. There has not been any consensus upon the duration of antibiotic administration, but it is a common practice among experts to administer antibiotics for 6 weeks after the last debridement. Serial measurement of inflammation markers such as ESR and CRP should also be performed to monitor treatment response.

**Table 3** Recommendations of antibiotic treatment for osteomyelitis

<table>
<thead>
<tr>
<th>Onset</th>
<th>Pathogen</th>
<th>Intravenous treatment of choice</th>
<th>Alternative intravenous treatment</th>
<th>Oral treatment or i.v.-to-p.o. switch</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute (initial therapy as in MSSA; treatment given according to culture results)</td>
<td><em>S. aureus</em> (MRSA)</td>
<td>Linezolid 600 mg (i.v.) every 12 hours for 4–6 weeks</td>
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<tr>
<td></td>
<td></td>
<td>or Quinupristin/dalfopristin 7.5 mg/kgBB (i.v.) every 8 hours for 4–6 weeks</td>
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<tr>
<td></td>
<td></td>
<td>or Minocyclin 100 mg (i.v.) every 12 hours for 4–6 weeks</td>
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<tr>
<td></td>
<td></td>
<td>or Vancomycin 2 g every 12 hours for 4–6 weeks</td>
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<tr>
<td></td>
<td><em>S. aureus</em> (MSSA)</td>
<td>Ceftriaxone 1 g every 24 hours for 4–6 weeks</td>
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<tr>
<td></td>
<td></td>
<td>or Meropenem 1 g (i.v.) every 8 hours for 4–6 weeks</td>
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<tr>
<td>Enterobacteriaceae</td>
<td>Ceftriaxone 1 g (i.v.) every 24 hours for 4–6 weeks</td>
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<tr>
<td></td>
<td>or Quinolones (ciprofloxacin 400 mg, levofloxacin 750 mg, gatifloxacin 400 mg, or moxifloxacin 400 mg) every 24 hours for 4–6 weeks</td>
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<td></td>
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<tr>
<td>Chronic (diabetes mellitus)</td>
<td>Group A or B streptococcus, <em>S. aureus</em> (MSSA), <em>E. coli</em>, <em>P. mirabilis</em>, <em>K. pneumoniae</em>, <em>B. fragilis</em>, <em>S. aureus</em> (MRSA)</td>
<td>Meropenem 1 g (i.v.) every 8 hours* or Piperacillin/tazobactam 3.375 mg (i.v.) every 6 hours* or Eratopenem 1 g (i.v.) every 8 hours* or combination therapy Ceftriaxone 1 g (i.v.) every 24 hours* with metronidazole 1 g (i.v.) every 24 hours*</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>or Moxifloxacin 400 mg (i.v.) every 24 hours*</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>or Ceftriaxone 2 g (i.v.) every 8 hours for 4–6 weeks</td>
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<td></td>
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<tr>
<td>Tuberculous osteomyelitis</td>
<td><em>M. tuberculosis</em></td>
<td>Treatment as in pulmonary tuberculosis for 6–9 months</td>
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</table>

*usually administered for 1 week after debridement or surgery.

**CONCLUSIONS**

Proper diagnosis in osteomyelitis is important since it determines the decision-making in the management of the disease. The clinical diagnosis of osteomyelitis may be complicated by several conditions, such as the presence of prosthesis, extensive ulcer, vascular insufficiency, or diabetes mellitus. Imaging techniques play important role in the diagnosis of osteomyelitis, but their results should be interpreted with care as they have a wide range of sensitivity and specificity. Conventional radiography, an affordable and widely available technique, has been proven to be useful in diagnosing and excluding the differential diagnoses of osteomyelitis. Surgical intervention to remove necrotic tissues and administration of antibiotics to eradicate pathogens are necessary in the management of osteomyelitis. Quinolones, rifampin, and clindamycin are some antibiotics that have been proven to have good penetration into bone.
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