

Diagnosis and management of osteomyelitis

Gunawan,¹ B Setiyohadi²

¹ Department of Internal Medicine, University of Indonesia School of Medicine/ Cipto Mangunkusumo General Hospital, Jakarta;

² Division of Rheumatology, Department of Internal Medicine, University of Indonesia School of Medicine/ Cipto Mangunkusumo General Hospital, Jakarta

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 “abscessus 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 immunosuppressive 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 (e.g. 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, preceding 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 (IFN γ), and tumor necrosis factor α (TNF α).^{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.^{3,4}

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

Anatomic type	
Stage 1: Medullary osteomyelitis	Infection only involves intramedullary surface of bone, e.g. in hematogenous infection and bone marrow infection.
Stage 2: Superficial osteomyelitis	True osteomyelitis, caused by direct inoculation or contiguous focus of infection after exposure of necrotic bone surface under damaged soft tissue.
Stage 3: Localized osteomyelitis	Marked by presence of thick sequestra on bone cortex; this could be removed surgically without disturbing bone stability.
Stage 4: Diffuse osteomyelitis	At this stage, bone resection is usually required to stop the infection; bone may lose its stability before or after the debridement.
Host physiological status	
Class A: normal hosts	
Class B: hosts with systemic or local condition	
Class C: hosts in whom treatment will cause greater morbidity than the disease itself	
Factors affecting immunity, metabolism, and local vascularization	
Systemic factors	Local factors
Malnutrition	Chronic lymphedema
Liver or kidney failure	Venous stasis
Diabetes mellitus	Disorders of large blood vessel
Chronic hypoxia	Arteritis
Immune disease	Disorders of small blood vessel
Malignancy	Extensive scar tissue
Extreme old age	Radiation fibrosis
Immune deficiency or immunosuppressive therapy	Neuropathy
	Heavy smoking (≥ 2 packs/day)

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.

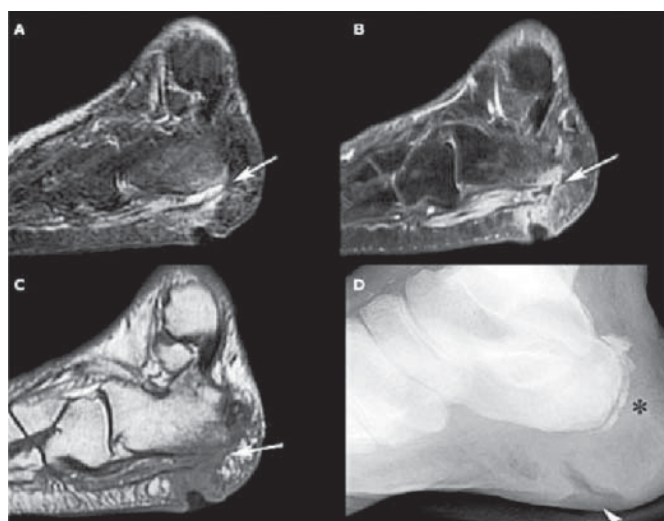


Figure 1 (A) Sagittal fluid-sensitive short-tau inversion recovery (STIR) image demonstrates high signal fluid collection along the plantar surface of the calcaneus (white arrow); (B) Sagittal postcontrast T1-weighted image with fat saturation demonstrates the peripherally enhancing fluid collection (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 calcaneus (white arrow). Osseous remodeling and periosteal reaction about the posterior calcaneus (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

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

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.^{34,35} Several in vitro studies showed that rifampin, clindamycin, and quinolones also penetrate well into bone.^{36,37} Use of prostheses may increase antibiotic resistance by formation of biofilms. Some experts suggest combination of rifampin with other antibiotics since there are high rates of resistance when it is used alone.³⁸

Antibiotics is usually given in long-term because there is persistence of *S. aureus* in osteoblasts, as has been showed by several animal studies.^{4,39} 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.⁴⁰

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.

Table 3 Recommendations of antibiotic treatment for osteomyelitis⁴¹

Onset	Pathogen	Intravenous treatment of choice	Alternative intravenous treatment	Oral treatment or i.v.-to-p.o. switch
Acute (initial therapy as in MSSA); treatment given according to culture results	<i>S. aureus</i> (MRSA)	Linezolid 600 mg (i.v.) every 12 hours for 4–6 weeks or Quinupristin/dalfopristin 7.5 mg/kgBB (i.v.) every 8 hours for 4–6 weeks or Minocyclin 100 mg (i.v.) every 12 hours for 4–6 weeks or Vancomycin 2 g every 12 hours for 4–6 weeks		Linezolid 600 mg (p.o.) every 12 hours for 4–6 weeks or Minocyclin 100 mg (p.o.) for 4–6 weeks
	<i>S. aureus</i> (MSSA)	Ceftriaxone 1 g every 24 hours for 4–6 weeks or Meropenem 1 g (i.v.) every 8 hours for 4–6 weeks	Cefotaxime 2 g (i.v.) every 6 hours for 4–6 weeks or Ceftizoxime 2 g (i.v.) every 8 hours for 4–6 weeks	Clindamycin 300 mg (p.o.) every 8 hours for 4–6 weeks or Cephalexine 1 g (p.o.) every 6 hours for 4–6 weeks or Quinolones (moxifloxacin 400 mg, levofloxacin 500 mg, or gatifloxacin 400 mg) every 24 hours for 4–6 weeks
	Enterobacteriaceae	Ceftriaxone 1 g (i.v.) every 24 hours for 4–6 weeks or Quinolones (ciprofloxacin 400 mg, levofloxacin 750 mg, gatifloxacin 400 mg, or moxifloxacin 400 mg) every 24 hours for 4–6 weeks	Cefotaxime 2 g (i.v.) every 6 hours for 4–6 weeks or Ceftizoxime 2 g (i.v.) every 8 hours for 4–6 weeks	Quinolones (ciprofloxacin 500 mg, levofloxacin 750 mg, moxifloxacin 400 mg, or gatifloxacin 400 mg) every 24 hours for 4–6 weeks
Chronic (diabetes mellitus)	Group A or B streptococcus, <i>S. aureus</i> (MSSA), <i>E. coli</i> , <i>P. mirabilis</i> , <i>K. pneumoniae</i> , <i>B. fragilis</i> , <i>S. aureus</i> (MRSA)	Meropenem 1 g (i.v.) every 8 hours* or Piperacilin/tazobactam 3.375 mg (i.v.) every 6 hours* or Ertapenem 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*	Moxifloxacin 400 mg (i.v.) every 24 hours* or Ceftizoxime 2 g (i.v.) every 8 hours* or Ampicillin/sulbactam 3 g (i.v.) every 6 hours* or combination therapy Clindamycin 600 mg (i.v.) every 8 hours with quinolones (i.v.) (ciprofloxacin 400 mg, levofloxacin 750 mg, gatifloxacin 400 mg, or moxifloxacin 400 mg)	Clindamycin 300 mg (p.o.) every 8 hours* with quinolones (i.v.)* or monotherapy Moxifloxacin 400 mg (p.o.) every 24 hours*
		Ceftriaxone 1 g (i.v.) every 24 hours for 2–4 weeks or Ceftizoxime 2 g (i.v.) every 8 hours for 2–4 weeks	Clindamycin 600 mg (i.v.) every 8 hours for 2–4 weeks with quinolones (i.v.) every 24 hours for 2–4 weeks	Clindamycin 300 mg (p.o.) every 8 hours for 2–4 weeks with quinolones (p.o.) every 24 hours for 2–4 weeks
Chronic (peripheral vascular disease, nondiabetic)	<i>S. aureus</i> , group A or B streptococcus, Enterobacteriaceae	Ceftriaxone 1 g (i.v.) every 24 hours for 2–4 weeks or Ceftizoxime 2 g (i.v.) every 8 hours for 2–4 weeks	Clindamycin 600 mg (i.v.) every 8 hours for 2–4 weeks with quinolones (i.v.) every 24 hours for 2–4 weeks	Clindamycin 300 mg (p.o.) every 8 hours for 2–4 weeks with quinolones (p.o.) every 24 hours for 2–4 weeks
Tuberculous osteomyelitis	<i>M. tuberculosis</i>	Treatment as in pulmonary tuberculosis for 6–9 months		

*usually administered for 1 week after debridement or surgery.

MSSA, methicillin-sensitive *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*; i.v., intravenous; p.o., per oral.

REFERENCES

- Berbari, EF, Steckelberg, JM, Osmon, DR. Osteomyelitis. In: Mandell GL, Bennet J, Dolin R, editors. Principles and practice of infectious diseases. 6th ed. Philadelphia: Elsevier; 2005. p. 1322.
- Lew DP, Waldvogel FA. Osteomyelitis. *Lancet* 2004;364:369–79.
- Mader JT, Shirliff M, Calhoun JH. Staging and staging application in osteomyelitis. *Clin Infect Dis* 1997;25:1303–9.
- Lew DP, Waldvogel FA. Osteomyelitis. *N Engl J Med* 1997;336:999–1007.
- Foster TJ, Höök M. Surface protein adhesins of *Staphylococcus aureus*. *Trends Microbiol* 1998;6:484–8.
- Herrmann M, Vaudaux PE, Pittet D, Auckenthaler R, Lew DP, Schumacher-Perdreau F, et al. Fibronectin, fibrinogen and laminin act as mediators of adherence of clinical staphylococcal isolates to foreign material. *J Infect Dis* 1988;158:693–701.
- Johansson, A, Flock, JI, Svensson, O. Collagen and fibronectin binding in experimental staphylococcal osteomyelitis. *Clin Orthop Relat Res* 2001;382:241–6.
- Yacoub A, Lindahl P, Rubin K, Wendel M, Heinegård D, Rydén C. Purification of a bone sialoprotein binding protein from *Staphylococcus aureus*. *Eur J Biochem* 1995;222:919–25.
- Rydén C, Tung HS, Nikolaev V, Engström A, Oldberg A. *Staphylococcus aureus* causing osteomyelitis binds to a nonapeptide sequence in bone sialoprotein. *Biochem J* 1997;327:825–9.
- Shirliff ME, Leid JG, Costerton JW. The basic science of musculoskeletal infections. In: Calhoun JH, Mader JT, editors. Musculoskeletal infections. New York: Marcel Dekker, Inc.; 2003. p. 1–62.
- Williams RJ, Smith RL, Schurman DJ. Septic arthritis. Staphylococcal induction of chondrocyte proteolytic activity. *Arthritis Rheum* 1990;33:533–41.
- Webb LX, Wagner W, Carroll D, Tyler H, Coldren F, Martin E. Osteomyelitis and intraosteoblastic *Staphylococcus aureus*. *J Surg Orthop Adv* 2007;16:73–8.
- Ellington JK, Harris M, Hudson MC, Vishin S, Webb LX, Sherertz R. Intracellular *Staphylococcus aureus* and antibiotic resistance: implications for treatment of staphylococcal osteomyelitis. *J Orthop Res* 2006;24:87–93.
- Greenberg DP, Bayer AS, Cheung AL, Ward JI. Protective efficacy of protein A-specific antibody against bacteremic infection due to *Staphylococcus aureus* in an infant rat model. *Infect Immun* 1989;57:1113–8.
- Littlewood-Evans AJ, Hattenberger MR, Lüscher C, Pataki A, Zak O, O'Reilly T. Local expression of tumor necrosis factor alpha in an experimental model of acute osteomyelitis in rats. *Infect Immun* 1997;65:3438–43.
- Schlievert PM. Role of superantigen in human disease. *J Infect Dis* 1993;167:997–1002.
- Newman LG, Waller J, Palestro CJ, Schwartz M, Klein MJ, Hermann G, et al. Unsuspected osteomyelitis in diabetic foot ulcers. Diagnosis and monitoring by leukocyte scanning with indium In-111 oxyquinoline. *JAMA* 1991;266:1246–51.
- Butalia S, Palda VA, Sargeant RJ, Detsky AS, Mourad O. Does this patient with diabetes have osteomyelitis of the lower extremity? *JAMA* 2008;299:806–13.
- Lipsky BA, Berendt AR, Deery HG, Embil JM, Joseph WS, Karchmer AW, et al. Diagnosis and treatment of diabetic foot infections. *Clin Infect Dis* 2004; 39:885–910.
- Darouiche RO, Landon GC, Klima M, Musher DM, Markowski J. Osteomyelitis associated with pressure sores. *Arch Intern Med* 1994;154:753–8.
- Horwich P. Approach to imaging modalities in the setting of suspected osteomyelitis. [Online]. 2010 [cited 2011 January]; Available from: URL: http://www.uptodate.com/contents/approach-to-imaging-modalities-in-the-setting-of-suspected-osteomyelitis?source=search_result&selecte dTitle=2~150#H4.
- Dinh, MT, Abad, CL, Safdar, N. Diagnostic accuracy of the physical examination and imaging tests for osteomyelitis underlying diabetic foot ulcers: meta-analysis. *Clin Infect Dis* 2008; 47:519-527. Durham JR, Lukens ML, Campanini DS, Wright JG, Smead WL. Impact of MRI on the management of diabetic foot infections. *Am J Surg* 1991;162:150–4.
- Tomas MB, Patel M, Marwin SE, Palestro CJ. The diabetic foot. *Br J Radiol* 2000;73:443–50.
- Gold RH, Hawkins RA, Katz RD. Bacterial osteomyelitis: findings on plain radiography, CT, MR, and scintigraphy. *AJR Am J Roentgenol* 1991;157:365–70.
- Kapoor A, Page S, Lavalley M, Gale DR, Felson DT. Magnetic resonance imaging for diagnosing foot osteomyelitis: a meta-analysis. *Arch Intern Med* 2007;167:125–32.
- Ledermann HP, Kaim A, Bongartz G, Steinbrich W. Pitfalls and limitations of magnetic resonance imaging in chronic posttraumatic osteomyelitis. *Eur Radiol* 2000;10:1815–23.
- Mader JT, Ortiz M, Calhoun JH. Update on the diagnosis and management of osteomyelitis. *Clin Podiatr Med Surg* 1996;13:701–24.
- Wing VW, Jeffrey RB Jr, Federle MP, Helms CA, Trafton P. Chronic osteomyelitis examined by CT. *Radiology* 1985;154:171–4.
- Seltzer SE. Value of computed tomography in planning medical and surgical treatment of chronic osteomyelitis. *J Comput Assist Tomogr* 1984;8:482–7.
- Schauwecker DS. The scintigraphic diagnosis of osteomyelitis. *AJR Am J Roentgenol* 1992;158:9–18.
- Schauwecker DS. Osteomyelitis diagnosis with In-111-labeled leukocytes. *Radiology* 1989;171:141–6.
- Perry M. Erythrocyte sedimentation rate and C reactive protein in assessment of suspected bone infection—are they reliable indices? *J R Coll Surg Edinb* 1996;41:116–8.
- Unkila-Kallio L, Kallio MJT, Eskola J, Peltola H. Serum CRP, erythrocyte sedimentation rate and WBC in acute hematogenous osteomyelitis of children. *Pediatrics* 1994;93:59–62.
- Lew DP, Waldvogel FA. Quinolones and osteomyelitis: state-of-the-art. *Drugs* 1995;49 Suppl 2:100–11.
- Huddleston PM, Steckelberg JM, Hanssen AD, Rouse MS, Bolander ME, Patel R. Ciprofloxacin inhibition of experimental fracture healing. *J Bone Joint Surg Am* 2000;82:161–73.
- Dworkin R, Modin G, Kunz S, Rich R, Zak O, Sande M. Comparative efficacies of ciprofloxacin, pefloxacin, and vancomycin in combination with rifampin in a rat model of methicillin-resistant *Staphylococcus aureus* chronic osteomyelitis. *Antimicrob Agents Chemother* 1990;34:1014–6.
- Norden CW. Experimental chronic staphylococcal osteomyelitis in rabbits: Treatment with rifampin alone and in combination with other antimicrobial agents. *Rev Infect Dis* 1983;5 Suppl 3:S491–4.
- Perlroth J, Kuo M, Tan J, Bayer AS, Miller LG. Adjunctive use of rifampin for the treatment of *Staphylococcus aureus* infections: a systematic review of the literature. *Arch Intern Med* 2008;168:805–19.
- Norden, CW. Lessons learned from animal models of osteomyelitis. *Rev Infect Dis* 1988;10:103–110.
- Trampuz, A, Zimmerli, W. Diagnosis and treatment of infections associated with fracture-fixation devices. *Injury* 2006;37 Suppl 2:S59–66.
- Cunha BA, Nichols RL, Rex JH, Cleri DJ, Schlossberg D. Osteomyelitis. In: Cunha BA, editor. Antibiotic essentials. 7th ed. Sudbury (USA): Jones and Bartlett Publishers; 2008. p. 200–1.