Relevance of Osteomyelitis to Clinical Practice

1

Caitlin S. Garwood and Paul J. Kim

Introduction

Osteomyelitis is one of the most devastating conditions of the foot and ankle, and it remains a challenge to the clinician in both diagnosis and treatment. The lower extremity tends to be more susceptible to infection due to thin soft tissue layers, potentially poor vascular supply, neuropathy, structural deformity, boney prominences, and poor fitting shoes. Trauma, diabetes, peripheral vascular disease, prosthetic implants, and bacteremia can all lead to debilitating infection within the bones of the lower extremity. Advances in diagnosis and treatment have helped promote limb salvage, but there is still a great risk of partial or complete limb loss once infection involves the skeletal framework. Osteomyelitis is considered to be one of the most difficult-to-treat infectious disease processes. Despite its devastating outcomes and relatively high prevalence, there is a wide disparity in its diagnosis and treatment. Thus, a consensus for the most appropriate modalities for diagnosis and the most effective methods for treatment is difficult to achieve. This chapter will introduce the topic of osteomyelitis of the foot and ankle and provide a broad construct for a more detailed discussion found in the remainder of this book. Osteomyelitis simply defined is inflammation of bone usually caused by an infectious source, as was first introduced by Nelaton in 1844 [1, 2]. When broken down into its components, "osteo-" means bone, "myelo-" means marrow, and "-itis" means inflammation. This very definition can cause confusion depending on the clinician's perspective and specialty. For example, a surgeon treating "osteomyelitis" assumes a clinical infectious process corroborated by the pathologist who diagnoses osteomyelitis histologically. The pathologist, however, is reporting elements of an inflammatory process and not necessarily infection. In other words, osteomyelitis can mean something different to each specialist. It is possible that the lack of consensus for definition of osteomyelitis can create an environment where necessary treatment may not be rendered. Further, other terms can add to the overall confusion in defining osteomyelitis or related diagnoses. In the literature, the term "osteitis" can be confused with osteomyelitis but usually refers to involvement of the cortex only, whereas osteomyelitis also invades the bone marrow. Similarly, "periosteitis" is an infectious process involving only the periosteum [1–4]. Osteomyelitis can involve only part of a single section of bone or may encompass multiple sections of a bone such as the periosteum, cortex, or marrow. It can also involve more than one bone, which is often the case when occurring from a septic joint, infected prostheses, or an infection resulting from Charcot neuroarthropathy.

Epidemiological data on osteomyelitis of the foot and ankle is not consistent or abundant. Most of the data available is focused on other parts of the body, such as the tibia or mandible. In addition, most of the research on foot and ankle osteomyelitis is developed around osteomyelitis present in diabetic foot ulcers, leaving minimal data related to trauma and other causes. The overall incidence of osteomyelitis is not generally high because healthy bone is normally resistant to infection. Waldvogel et al. in 1970 reported that 19 % of osteomyelitis cases were due to hematogenous spread, 47 % from contiguous-focus, and 34 % were associated with vascular insufficiency [5, 6]. Currently the incidence of new cases of hematogenous, pediatric osteomyelitis is 2.9–22 per 100,000 patients [7–9]. The overall incidence of bone and joint infections in adults is 54.6 per 100,000 as was reported in 2012 [10]. It is still thought that today the majority of cases, particularly in adults, are contiguous-focus osteomyelitis especially with the dramatic rise in the diabetic population. As far as posttraumatic osteomyelitis, 2–16 % of open fractures are associated with bone infection depending on the extent and severity of the injury [11–13].

C.S. Garwood, D.P.M. • P.J. Kim, D.P.M., M.S., F.A.C.F.A.S. (✉)
Department of Plastic Surgery, Center for Wound Healing & Hyperbaric Medicine, Georgetown University Hospital, 3800 Reservoir Rd, NW, Bles 1st Floor, Washington, DC 20007, USA
e-mail: caitlin.garwood@gmail.com; paul.j.kim@gunet.georgetown.edu

T.J. Boffeli (ed.), *Osteomyelitis of the Foot and Ankle*, DOI 10.1007/978-3-319-18926-0_1

Currently 382 million people worldwide are living with diabetes [14]. The risk of foot ulceration in diabetic patients is as high as 25 % and approximately 20–68 % of these ulcerations are reported to be complicated by osteomyelitis [15–21]. Osteomyelitis brings a significant risk of amputation whether it is a single digit, total ray, transmetatarsal, or lower limb and the rate of amputation has been reported to be up to 66 % [16, 21–23].

Etiology and Classification

Ideally, classifying osteomyelitis should incorporate all possible etiologies as well as address the various timing of the disease. Further, it is helpful when a classification system includes suggestions for treatment. Due to the different types of osteomyelitis, several classification schemes have been developed.

Osteomyelitis is broadly categorized into acute, subacute, or chronic based on timing and presentation of the disease process. Acute bone infection develops over several days to weeks, with 2 weeks being the most accepted time frame [5, 6, 24]. Chronic osteomyelitis has been defined arbitrarily as evolving or lasting over several months, with 6 months being the most widely accepted period [5, 6, 25, 26]. Any infection lingering between 2 and 6 months would then be classified as subacute. The temporal definitions are imprecise and confusing especially when there might be evidence of necrotic and chronic changes in the bone only one week after presentation. Others have defined "acute" as the first presentation of osteomyelitis in a particular bone and "chronic" as a recurrence of the infection that had previously been treated. Categorizing osteomyelitis as "initial" and "recurrent" may be more useful for the clinician in terms of implementing a proper treatment regimen [2, 3].

Osteomyelitis can be classified based on the cause whether by direct extension, hematogenous spread through contamination of the bloodstream, or contiguous spread from a current site of infection [27]. Direct extension osteomyelitis encompasses bone infections that arise from either a puncture wound or elective surgery that exposes bone to an infectious contaminant. It has been reported in the literature that 2 % of puncture wounds lead to osteomyelitis [28, 29]. Hematogenous osteomyelitis occurs from the seeding of bacteria from a distant site or bacteremia that spreads through the vascular system [26, 30]. It is thought to be primarily a pediatric disease with 85 % of the cases occurring in patients 17 years of age or younger [31]. It can also occur in the elderly or intravenous drug abusers. The last etiology is contiguous spread which includes bone infections that start from a soft tissue infection including open fractures, decubitus ulcers, or diabetic foot ulcers.

Two classification systems are commonly used throughout the literature and are important in understanding osteomyelitis. Other classifications have been described but are not used in common practice (Table 1.1). Waldvogel in 1970 developed a classification based on the duration of the disease, the mechanism of infection, and presence or absence of vascular insufficiency [5, 32]. A short coming of this classification system is that it provides no therapeutic guidelines (Table 1.2). Cierny and Mader developed a classification that is most applicable to long and large bones and has been seen as difficult to apply to digital bones or other small bones in the foot. It is based on the area of bone infected and the physiological status of the host and also incorporates the dynamic nature of the disease, which is useful to the clinician (Table 1.3) [25, 32, 33].

Table 1.1 Classification schemes for osteomyelitis [5, 33, 121]

Reference	Classification	Overview
[5], see Table 1.2	"Waldvogel"	• Mechanism – Hematogenous – Contiguous – Vascular compromise • Duration – Acute – Chronic
[33], see Table 1.3	"Cierny-Mader"	• Anatomic – Medullary – Superficial – Localized – Diffuse • Physiologic – Normal host – Compromised – Prohibitive
[121]	"Buckholtz"	1. Wound induced 2. Mechanogenic infection 3. Physeal osteomyelitis 4. Ischemic limb disease 5. Combinations of 1–4 6. Osteitis with septic arthritis 7. Chronic osteitis/osteomyelitis

Table 1.2 Waldvogel classification of osteomyelitis [5, 6, 31]

	Type	Characteristics
Mechanism of bone infection	Hematogenous	Seeding of bacteria from a distance source that spreads through the bloodstream
	Contiguous	Infection from an adjacent site such as open fracture
	Associated with vascular compromise	Infections in patients with peripheral vascular disease or diabetes
Duration of infection	Acute	Initial diagnosis of osteomyelitis. Edema, abscess, vascular congestion, small vessel thrombosis
	Chronic	Prolonged or recurrence of acute case
		Ischemia, necrosis, sequestra

Table 1.3 Cierny-Mader staging system for osteomyelitis [26, 31–33]

	Stage	Name	Characteristics	Clinical example(s)
Anatomic type	I	Medullary	Infection restricted to the bone marrow	1. Infected intramedullary rod
				2. Hematogenous osteomyelitis
	II	Superficial	Infection restricted to outer cortex	Diabetic foot ulcer with infection extending to bone
	III	Localized	Well demarcated, full-thickness lesion without instability	Progression from Stage I or II
	IV	Diffuse	Infection spread to entire bone circumference with instability	Progression from Stage I, II, or III
Physiologic class	A	Normal host	No comorbidities	
	B	Bs	Systemic compromise	Diabetes, malnutrition, renal failure, hepatic failure, malignancy, extremes of age, immune disease
		Bl	Local compromise	Smoking, chronic lymphedema, major or small vessel compromise, venous stasis, arthritis, large scars, neuropathy
		Bls	Systemic and local compromise	Combination of above factors
	C	Prohibitive/poor clinical conditions	Treatment has a higher risk than osteomyelitis itself	Patient who is not a surgical candidate or who cannot tolerate long-term antibiotics

Pathophysiology and Microbiology

The pathophysiology of osteomyelitis is complicated but a basic understanding can help in the diagnosis and treatment of this disease. Throughout the natural course of osteomyelitis osseous changes occur, biofilm forms, and neutrophils cause major defects. All forms of osteomyelitis begin by bacteria adhering to the bone matrix via receptors to fibronectin, fibrinogen, laminin, collagen, and proteins [4, 34–37]. The attached organisms cause an inflammatory response of the bone. As inflammation persists and intramedullary pressure rises, the vascular channels become obliterated causing patches of ischemia and bone necrosis. These areas of necrotic bone can detach from the bone and are called sequestra [4, 25, 26, 34–38]. As necrotic bone is forming, osteoclastic activity is stimulated by inflammatory factors such as interleukin-1 and tumor necrosis factor. This causes loss of bone and creates a destructive appearance of the bone. At the same time, a periosteal reaction begins and causes new bone formation. This surrounds and encases the sequestrum and is termed involucrum. During the process of bone formation and destruction cloaca form, which are openings in the involucrum that connect to the sequestrum. It is through the cloaca which exudate often extrudes [3, 38].

Bacteria are able to fend off host defenses as well as antibiotics through the formation of biofilm, and thus infections can persist even after medical or surgical treatments. Biofilms are colonies of pathogens that bind to the surfaces of wounds or implants. They are generally composed of 25–30 % pathogen and 70–75 % self-secreted amorphous matrix [34–39]. A wound bed is an ideal environment for biofilm to form since it is moist and nutritionally supportive. Biofilm also tends to form on devitalized tissue and bone, such as involucrum [38]. It has been reported that as rapidly as 10 h, many of the bacteria flora present on the skin can form a biofilm [40]. They generally are polymicrobial in nature with anaerobes, *Serratia*, *Staphylococcus*, and *Pseudomonas* being the most robust [38–41]. In addition to multiple species present, there are various mechanisms by which a biofilm inhibits wound healing and can make the host more susceptible to osteomyelitis. The matrix created by the biofilm itself creates a physical barrier that inhibits host inflammatory cells from ridding the body of the pathogens. Biofilms are highly resistant to antibiotics as they do not easily penetrate through this matrix. Also, there is a metabolically senescent nature of biofilm, which leads to further resistance since many antibiotics target rapidly dividing bacteria [35, 39, 41]. Thus, it has become increasingly important to treat and extinguish the biofilm in a wound, on the surface of hardware (screws, plates, suture, joint implants), or on exposed bone in order to fully treat or prevent osteomyelitis.

Most foot and ankle osteomyelitis is polymicrobial in nature, except hematogenous osteomyelitis, which is almost always monomicrobial [38]. As with soft tissue infections, the causative agent in bone infections is primarily bacterial but can also result from fungal, parasitic, viral, or mycobacterial infections (Table 1.4) [32, 42]. *Staphylococcus aureus* is the most prevalent causative organism in osteomyelitis [4, 43]. It accounts for the majority of hematogenous osteomyelitis in children and adults and is present in many other foot and ankle cases. *S. aureus* has a number of unique traits that make it particularly virulent. First, it contains factors that allow it to attach to extracellular matrix proteins contributing to early colonization of the host. *S. aureus* also has features such as toxins and capsular polysaccharides that make it less susceptible to host defenses. Osteolysis has been seen to occur rapidly from the increased osteoclastic activity due to the release of tumor necrosis factor-α, prostoglandins, and

Table 1.4 Most commonly associated microorganism and their clinical setting [4, 25, 32]

Common clinical setting	Etiology
Hematogenous, all ages	*Staphylococcus aureus*
Hematogenous, infants/children	*Haemophilus influenzae*
Diabetes mellitus, vascular insufficiency, contaminated open fracture	Polymicrobial: *Staphylococcus aureus*, *B-Hemolytic Streptococci*, *Enterococci*, aerobic gram-negative bacilli
Orthopedic implant devices, hardware, foreign bodies	*Staphylococcus aureus*, coagulase-negative staphylococci (*Staphylococcus epidermidis*)
Human or animal bites	*Pasteurella multocida*, *Eikenella corrodens*
Puncture wounds on the foot	*Pseudomonas aeruginosa*
Soil contamination	*Clostridium* sp., *Bacillus* sp., *Stenotrophomonas maltophilia*, *Nocardia* sp., atypical mycobacteria, *Aspergillus* sp., *Rhizopus* sp., *Mucor* sp.
Sickle-cell disease	*Salmonella* sp.
Intravenous drug users	*Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Candida* sp.

interleukin-1. It is the combination of these factors that makes *S. aureus* a common culprit in chronic infections leading to osteomyelitis [25, 26, 32, 35, 38]. Of great importance in foot and ankle osteomyelitis is the increasing prevalence of methacillin-resistant *S. aureus* (MRSA). This pathogen is frequently encountered in hospitalized patients along with other multidrug-resistant organisms. In 2013, it was reported that the incidence of community acquired MRSA was 1.6–29.7 cases per 100,000 and 2.8–43 % of those were bone and joint infections [44]. It has also been reported to account for 15.3 % of osteomyelitis cases in diabetic foot infections [26, 45, 46]. This rise in incidence throughout the general population, not just diabetic patients, has prompted clinicians to use broad-spectrum antibiotics prior to culture results. The treatment of MRSA osteomyelitis can be more prolonged and complicated with increasing lengths of hospital stays and complications [44, 45].

Pseudomonas aeruginosa is another common organism seen in osteomyelitis of the foot. It is frequently seen as the infecting organism in plantar puncture wounds since it is present on the soles of shoes and its predilection for warm, moist environments. It has been reported that osteomyelitis complicates 1.8–6.4 % of puncture wounds sustained to the feet [2, 26, 47–49]. In 2.5–14.6 % of diabetic foot osteomyelitis, *P. aeruginosa* has been isolated and is associated with a higher rate of recurrence and amputation than *S. aureus* [26, 46]. Thus, *P. aeruginosa* may be a more problematic and underappreciated organism in osteomyelitis.

Populations at Risk

Osteomyelitis behaves differently in various patient populations as well as different anatomical locations. There are cohorts of patients that are at a higher risk of developing a bone infection and situations where the clinician needs a higher index of suspicion for the disease. Recognizing patients and clinical situations with a high predilection for developing osteomyelitis will help the clinician with early diagnosis and an appropriate treatment protocol.

As mentioned previously, hematogenous osteomyelitis most frequently occurs in children. Those with an even higher risk factor are children with sickle-cell disease [50]. Due to obstruction and damage to the spleen, they are at an extreme susceptibility to infection. Risk factors in adults include intravenous drug use as well as common causes of bacteremia. These include urinary tract infections, indwelling catheters, central intravenous lines, and hemodialysis [2].

Recent trauma or surgery can put a patient at a higher risk of developing osteomyelitis. Any foot and ankle surgery can lead to a deep infection involving the bone. An incisional dehiscence, if not treated appropriately and in a timely fashion, can cause a debilitating infection in the bone. Likewise, implanted devices including plates, joint implants, and external fixators bring a higher risk factor simply by introducing a foreign material into the body. These implanted devices due to its contact on the bone surface can provide an optimal environment for biofilm formation, which in turn can cause infection of the underlying bone [51]. Patients who sustain an open fracture are more susceptible to osteomyelitis until the bone is covered with a soft tissue envelope. The longer the bone is exposed, the more likely the chance of developing a complication [52]. It is recommended that definitive soft tissue reconstruction take place within 7 days of injury and ideally by day 3, to minimize the risk of reconstructive failure or deep infections [52–54]. Injuries to the nail plate can also increase the risk of bone infection, particularly in pediatric patients because of the lack of soft tissue between the nail and the underlying bone [2, 55, 56]. Puncture wounds to the foot as well as animal or human bites can predispose the bone to infection [48, 49].

Complicating factors such as peripheral neuropathy, peripheral vascular disease, and underlying immunocompromise can lead to foot ulcerations. Wound chronicity can eventually lead to deep ulcers that penetrate to the level of the bone. It is important for high-risk patients, such as diabetics,

to minimize ulcerations by appropriate foot care and prevention [22, 23, 57]. Peripheral vascular disease (PVD), which is encountered in diabetic patients as well as tobacco abusers, is another risk factor. With decreased blood circulation to the foot or ankle, patients are at a higher risk of developing a wound [58]. The lack of blood flow creates a recalcitrant wound healing environment and the patients are at a higher risk for osteomyelitis. Often, patients will have both diabetes and PVD and have a 2- to 5.5-fold increase risk of ulceration leading to osteomyelitis [15, 59]. Patients with an impaired immune function may not have the ability to appropriately fight off an infection and thus are at a higher statistical risk of developing a deep bone infection. This includes patients taking corticosteroids for rheumatic or dermatologic diseases, patients receiving chemotherapy, organ transplant recipients, as well as systemic diseases like diabetes [25, 58, 60]. Uncontrolled diabetics live in a state of elevated glucose levels which impairs leukocyte function and can negatively affect the body's ability to respond to antimicrobials [60].

The lower extremity itself is a risk factor for developing osteomyelitis and is well known to be a hard-to-treat anatomical location. The foot and ankle has a relatively thin soft tissue envelope covering deep anatomical structures. This makes the lower extremity highly susceptible to repetitive trauma especially in areas of boney prominences. Once bone is exposed, soft tissue coverage can be challenging. There are very limited options for local tissue coverage in the lower extremity. Surgeons have thus turned to free tissue transfer to increase soft tissue girth, but the complexity of these procedures can lead to significant complications in many patients, especially in the elderly or patients with diabetes, peripheral vascular disease, end stage renal disease, or infection [61, 62]. In addition, instability is often created when bone is resected from the foot or when partial amputations are performed. This creates a dysfunctional lower extremity and can also lead to other problems including new ulcerations. As mentioned previously, many patients with foot osteomyelitis have poor vascular supply and the inability to heal. Rather than undergoing numerous limb salvage procedures when osteomyelitis is involved, patients may be better served with a below-knee or above-knee amputation [61–66].

Diagnosis

A unique challenge with osteomyelitis is *definitively* diagnosing the disease and making this diagnosis early. An accurate diagnosis is needed in order to formulate an appropriate treatment plan which is especially true for this progressive destructive process. There are several modalities used for identifying osteomyelitis including history, physical examination, laboratory values, imaging, microbiology, and bone biopsies (Fig. 1.1) [20, 67–81]. Ultimately, a combination of these modalities is needed to diagnose osteomyelitis. Each diagnostic modality has its own strengths and weaknesses with no single modality providing conclusive evidence of bone infection. To date, no single, robust, consensus-driven, diagnostic algorithm is available for clinicians to utilize for osteomyelitis. Since there is no standardized method available, ambiguous results and potentially failure of treatment can result.

An adequate history can be very informative for raising the suspicion and approaching a diagnosis of osteomyelitis. Frequent symptoms can include redness, swelling, pain, or drainage from a wound or surgical site. Often the pain is described as vague, deep, and chronic [4]. Any history of trauma or ulceration should be thoroughly investigated. Past medical history should be evaluated as well for systemic diseases and their current management and control. For example, it is important to evaluate glycemic control in diabetic patients. Other useful information includes nutritional status, ambulatory status, age, and presence of neuropathic or peripheral vascular symptoms [4, 26].

Physical examination and laboratory values for infection are two other commonly utilized modalities for the diagnosis of osteomyelitis. The physical signs of osteomyelitis are subjective in nature. This includes signs of infection of the overlying soft tissue envelope as well as the quality of the suspected area of bone infection. Fragmentation, necrosis, desiccation, and frank purulence of the bone are strong indicators of infection. However, these signs may not be specific for osteomyelitis. Fragmentation could be due to other factors including nutrition, age, Charcot neuro-osteoarthropathy, and trauma. Necrosis and desiccation could be the result of vascular compromise. Further, frank purulence may not be coming from the bone but from the surrounding soft tissue infection. The Grayson study recommended the "probe-to-bone" test for the diagnosis for osteomyelitis [19]. They reported a sensitivity of 66 %, specificity of 85 %, and a positive predictive value of 89 % with probe-to-bone test and presence of osteomyelitis. However, a subsequent study by Lavery et al. called into question the specificity for this test [68]. Their diagnosis had been confirmed with a bone culture and they found a sensitivity of 87 %, specificity of 91 %, positive predictive value of only 57 %, but a negative predictive value of 98 %. This shows that a negative probe-to-bone test may be more useful in excluding osteomyelitis than a positive test would be for confirming diagnosis. Elevated laboratory values including C-Reactive Protein, erythrocyte sedimentation rate, and white blood cell counts may be surrogate indicators of bone infection but lack specificity for osteomyelitis [82–84].

One of the major problems with diagnosing osteomyelitis is that imaging studies have low sensitivity to early detection and are non-specific. Plain radiographs, nuclear medicine studies, and magnetic resonance imaging are among the most

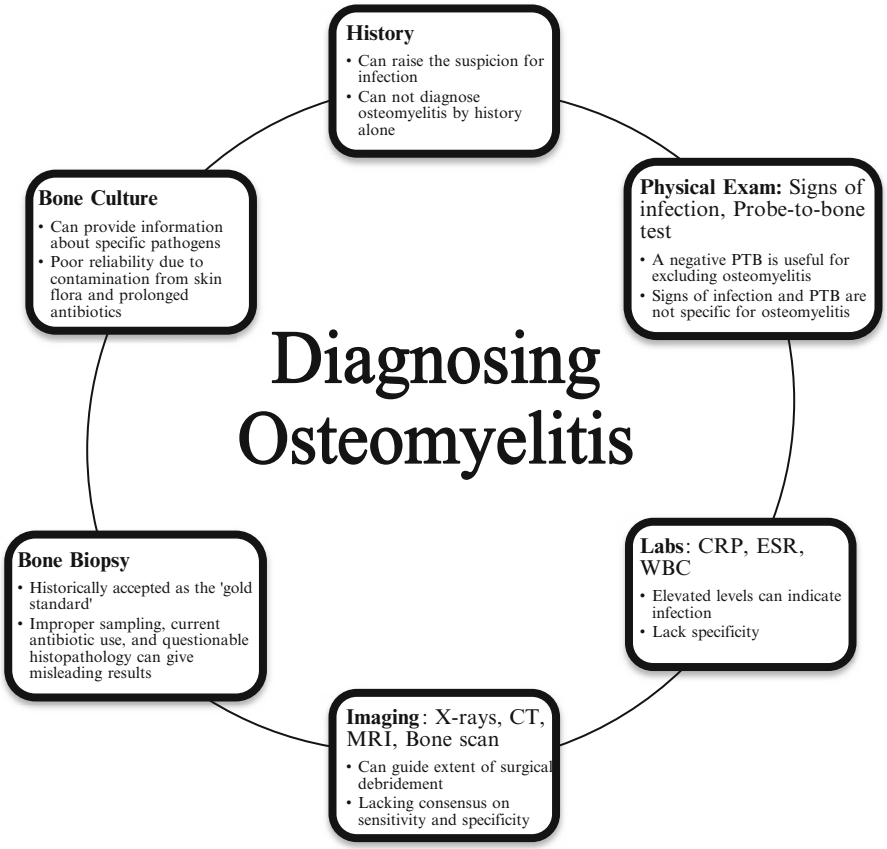

Fig. 1.1 Modalities used for diagnosing osteomyelitis. Each box represents a different modality with key points listed below. It is designed to represent the fact that several tools are used in combination to formulate the diagnosis of osteomyelitis [4, 19, 20, 26, 67–87]

commonly used imaging modalities for the diagnosis of osteomyelitis. Several studies have looked at the sensitivity and specificity of each without reaching a consensus on appropriate imaging [20, 67, 70–79, 85]. The second major issue is the difficulty in distinguishing between osteomyelitis and a different disease entity. This is especially troubling to the foot and ankle surgeon when dealing with diabetic patients. Sixty to seventy percent of diabetic patients have mild to moderate peripheral neuropathy and are at risk of developing neuro-osteoarthropathy [88, 89]. Charcot neuro-osteoarthropathy of the foot can often be mistaken for osteomyelitis both on physical examination as well as on imaging. Even more of a challenge is when both disease entities are present concomitantly.

Bone biopsy and bone culture are also commonly used to definitively diagnose osteomyelitis. In fact, it has long been purported that a bone biopsy is the gold standard for diagnosing osteomyelitis. However, it is not without its own challenges and problems due to improper sampling techniques, current use of antibiotics, or questionable histopathology results [80]. A study by Meyr et al. evaluated the reliability of histopathology of bone biopsies used for diagnosis of osteomyelitis in diabetic patients. They found a unanimous agreement between four board-certified pathologists for only 33.33 % of the specimens examined. Questionable results where at least one pathologist diagnosed "no evidence of OM" and at least one other pathologist diagnosed "findings consistent with OM," occurred 41.03 % of the time [80]. Further, as discussed in a previous paragraph, osteomyelitis may be used as a descriptive histological term that may or may not indicate infection, rather than a diagnosis. Bone tissue cultures also pose an issue with specimen contamination and only specific bacteria being cultured [86, 87]. There is a risk of false-positive results from skin flora surrounding the bone, but also a risk of false-negative results due to prolonged release of antibiotics from bone [87]. Thus, there is poor reliability of bone cultures taken in the presence of a wound in determining the diagnosis of osteomyelitis as well as the infecting pathogen.

Management

The ideal management of osteomyelitis depends on several factors specific to each patient and circumstance. Both medical and surgical methods are available and often a combination of therapies is necessary (Fig. 1.2). The goal of treatment is to eliminate infection and to prevent the development of a chronic infection or recurrence. A team approach to treatment

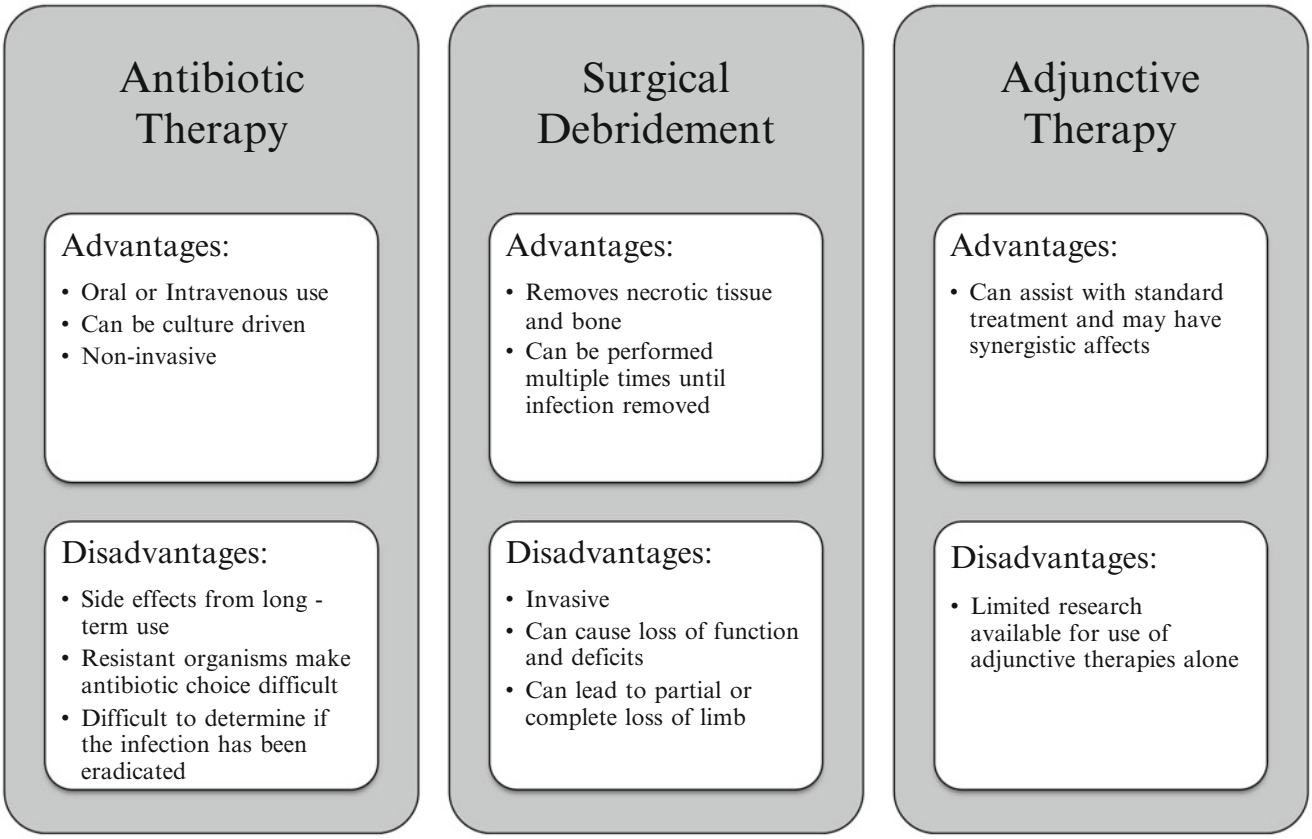

Fig. 1.2 Management of osteomyelitis. The advantages and disadvantages of antibiotic therapy, surgical debridement, and adjunctive therapy [2, 25, 92–107]

is often employed and includes specialty care for wound management, surgical debridement, antibiotic therapy, vascular optimization, and soft tissue or limb reconstruction [18, 57, 90, 91].

It has long been accepted that 4–6 weeks of parenteral antibiotics is the standard course of treatment for osteomyelitis. This theory, however, was largely drawn from animal models as well as observational data with randomized patient trials lacking [2]. The choice of antibiotics should be pathogen-driven while taking into consideration bone penetration, long-term side effects, and cost-effectiveness. Oral antibiotics are now being seen as an acceptable alternative to parenteral treatment as several antibiotics have excellent oral bioavailability with good bone penetration. Some oral antibiotics with acceptable oral bioavailability commonly include linezolid, fluoroquinolones, and clindamycin. Many have also employed a combination therapy where parenteral antibiotics are initiated for approximately 2 weeks followed by a prolonged course of oral antibiotics [2, 25, 92–94]. A recent Cochrane Review showed no statistically significant difference in terms of remission for patients treated with oral versus parenteral antibiotics. They also found no or insufficient evidence in terms of optimal length of treatment or medication [93].

Surgical debridement of bone infection is of significant importance in situations in which antibiotic therapy is not adequate, abscess or necrotic tissue is present, or systemic illness or sepsis mandates surgical intervention. A surgical plan is formulated based on the site and extent of infection as well as preservation of a functional limb. A surgeon must remove all necrotic bone and soft tissue which can frequently leave large deficits of bone or lead to minor or major amputation. After adequate debridement, there may be the need for boney stabilization or soft tissue reconstruction and coverage [93, 95–97]. Antibiotic impregnated spacers are also used to elute antibiotics over time in an area where infected bone was resected [98]. It has been seen useful for salvage after osteomyelitis, most frequently in the forefoot, in patients who would have otherwise received an amputation [98–100].

Another adjunctive therapy is the use of hyperbaric oxygen (HBO) therapy for chronic osteomyelitis. HBO therapy increases the oxygen tension of tissue and bone and has been shown to have several proposed effects on wound healing and osteomyelitis including improved leukocyte function, increased osteoclastic activity, and neovascularization [2, 26, 101, 102]. Although there is some proven efficacy when used in conjunction with other treatment modalities, strong

evidence is lacking on the success or efficacy of HBO therapy, especially when used alone and not with antibiotics or surgery [2, 101–107].

The combination of antibiotic therapy with surgical debridement has proven to be successful for long-term outcomes. It has not been proven whether surgical debridement alone would be adequate to prevent remission. Some authors believe that inadequate debridement is correlated with higher rates of recurrence [93, 96, 97, 108, 109]. Others report that antibiotic therapy can be shortened after debridement [110, 111]. Ultimately, a combination of therapies is most widely used and the clinician must make the decision based on each unique clinical situation.

Outlook

Unfortunately for patients affected by osteomyelitis of the foot and ankle, amputation can be an end result. This can include digital, partial ray, transmetatarsal, midfoot, below-knee or above-knee amputations. Amputations can have a great impact on a patient psychologically and in terms of their quality of life [112–116]. Digital and partial foot amputations alter the biomechanics of the foot and can lead to difficulty in ambulation or new ulcer formation and recurrence. Major amputations come wrought with complications as well including inability to ambulate, increased energy expenditure, and increase risk of mortality. It has been reported that a major leg amputation has a mortality rate of 52–70 % at 2 and 5 years [117, 118]. Every attempt should be made to preserve pedal function; however for some patients, the benefit of amputation out-weighs the risk of long-term antibiotics or multiple salvage surgeries. The overall recurrence rate of osteomyelitis remains at about 20–30 % in a patient's lifetime. In certain situations, such as with *P. aeruginosa*, the recurrence rate is as high as 50 % [93, 119, 120]. Patients who have osteomyelitis are considered to have a lifetime risk of recurrence at the same site of previous infection due to alterations to the bone surfaces and health.

Conclusion

Osteomyelitis of the foot and ankle is a major public health problem. With the rise in bacterial resistance to antibiotics as well as the lack of new antibiotics in the development pipeline, judicious use is required. However, there is a lack of consensus on the most appropriate methods for diagnosis and treatment of osteomyelitis. Thus, antibiotics may be used inappropriately. Surgical options for the treatment of osteomyelitis including resection, removal of hardware, and amputation also have problems. The lack of skeletal integrity compromises the functional capabilities of the foot and ankle. Experienced clinicians recognize that current diagnostic and treatment modalities fall short of providing a definitive answer. The following chapters provide a detailed discussion on the current evidence as well as valuable insight for the diagnosis and treatment of osteomyelitis.

References

1. Oloff L, Schulhofer S. Osteomyelitis. In: Banks A, Downy M, Martin D, Miller S, editors. McGlamry's comprehensive textbook of foot and ankle surgery. 3rd ed. Philadelphia: Lippincott, Williams & Wilkins; 2001.
2. Oloff LM, Heard GS. Osteomyelitis. In: Southerland JT, Boberg JS, Downey MS, Nakra A, Rabjohn LV, editors. McGlamry's comprehensive textbook of foot and ankle surgery. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2012.
3. Baltensperger M, Eyrich G. Osteomyelitis of the jaws. Lepzig: Springer; 2009.
4. Chihara S, Segreti J. Osteomyelitis. Dis Mon. 2010;56(1):5–31.
5. Waldvogel FA, Medoff G, Swartz MN. Osteomyelitis: a review of clinical features, therapeutic considerations and unusual aspects. N Engl J Med. 1970;282:198–206.
6. Waldvogel FA, Vasey H. Osteomyelitis: the past decade. N Engl J Med. 1980;303(7):360–70.
7. Blyth MJ, Kincaid R, Craigen MA, Bennet GC. The changing epidemiology of acute and subacute haematogenous osteomyelitis in children. J Bone Joint Surg Br. 2001;83(1):99–102.
8. Stoesser N, Pocock J, Moore CE, Soeng S, Hor P, Sar P, et al. The epidemiology of pediatric bone and joint infections in Cambodia, 2007–2011. J Trop Pediatr. 2013;59(1):36–42.
9. Grammatico-Guillon L, Maakaroun Vermesse Z, Baron S, Gettner S, Rusch E, Bernard L. Paediatric bone and joint infections are more common in boys and toddlers: a national epidemiology study. Acta Paediatr. 2013;102(3):e120–5.
10. Grammatico-Guillon L, Baron S, Gettner S, Lecuyer A, Gaborit C, Rosset P, et al. Bone and joint infections in hospitalized patients in France, 2008: clinical and economic outcomes. J Hosp Infect. 2012;82(1):40–8.
11. Browner BD. Skeletal trauma basic science, management, and reconstruction. In: Browner BD, editor. MD Consult. 4th ed. Philadelphia: Saunders/Elsevier; 2009.
12. Mader JT, Cripps MW, Calhoun JH. Adult posttraumatic osteomyelitis of the tibia. Clin Orthop Relat Res. 1999;360:14–21.
13. Roesgen M, Hierholzer G, Hax PM. Post-traumatic osteomyelitis. Pathophysiology and management. Arch Orthop Trauma Surg. 1989;108(1):1–9.
14. International Diabetes Federation. IDF diabetes atlas. 6th ed. Brussels, Belgium: International Diabetes Federation; 2013. http://www.idf.org/diabetesatlas.
15. Lavery LA, Armstrong DG, Wunderlich RP, Mohler MJ, Wendel CS, Lipsky BA. Risk factors for foot infections in individuals with diabetes. Diabetes Care. 2006;29:1288–93.
16. Singh N, Armstrong DG, Lipsky BA. Preventing foot ulcers in patients with diabetes. JAMA. 2005;293:217–28.
17. Lipsky BA, Berendt AR, Deery HG, et al. Diagnosis and treatment of diabetic foot infections. Clin Infect Dis. 2004;39(7):885–910.
18. Shank CF, Feibel JB. Osteomyelitis in the diabetic foot: diagnosis and management. Foot Ankle Clin. 2006;11(4):775–89.
19. Grayson ML, Gibbons GW, Balogh K, Levin E, Karchmer AW. Probing to bone in infected pedal ulcers. A clinical sign of underlying osteomyelitis in diabetic patients. JAMA. 1995;273(9):721–3.

20. 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(9):1246–51.
21. Balsells M, Viade J, Millan M, Garcia JR, Garcia-Pascual L, del Pozo C, et al. Prevalence of osteomyelitis in non-healing diabetic foot ulcers: usefulness of radiologic and scintigraphic findings. Diabetes Res Clin Pract. 1997;38(2):123–7.
22. Hartemann-Heurtier A, Senneville E. Diabetic foot osteomyelitis. Diabetes Metab. 2008;34(2):87–95.
23. Game FL. Osteomyelitis in the diabetic foot: diagnosis and management. Med Clin North Am. 2013;97(5):947–56.
24. Hatzenbuehler J, Pulling TJ. Diagnosis and management of osteomyelitis. Am Fam Physician. 2011;84(9):1027–33.
25. Lew DP, Waldvogel FA. Osteomyelitis. Lancet. 2004;364(9431):369–79.
26. Lindbloom BJ, James ER, McGarvey WC. Osteomyelitis of the foot and ankle: diagnosis, epidemiology, and treatment. Forthcoming: Foot Ankle Clin N AM; 2014. http://dx.doi.org/10.1016/j.fcl.2014.06.012.
27. Harmer JL, Pickard J, Stinchcombe SJ. The role of diagnostic imaging in the evaluation of suspected osteomyelitis in the foot: a critical review. Foot (Edinb). 2011;21(3):149–53.
28. Ansari MA, Shukla VK. Foot infections. Int J Low Extrem Wounds. 2005;4(2):74–87.
29. Malizos KN, Gougoulias NE, Dailiana ZH, Varitimidis S, Bargiotas KA, Paridis D. Ankle and foot osteomyelitis: treatment protocol and clinical results. Injury. 2010;41:285–93.
30. Kelsey R, Kor A, Cordano F. Hematogenous osteomyelitis of the calcaneus in children: surgical treatment and use of implanted antibiotic beads. J Foot Ankle Surg. 1995;34(6):547–55.
31. Lima AL, Oliveira PR, Carvalho VC, Cimerman S, Savio E. Recommendations for the treatment of osteomyelitis. Braz J Infect Dis. 2014;18(5):526–34. http://dx.doi.org/10.1016/j.bjid.2013.12.005.
32. Sia IG, Berbari EF. Osteomyelitis. Best Pract Res Clin Rheumatol. 2006;20(6):1065–81.
33. Cierny 3rd G, Mader JT, Penninck JJ. A clinical staging system for adult osteomyelitis. Clin Orthop Relat Res. 2003;414:7–24.
34. Uçkay I, Pittet D, Vaudaux P, Sax H, Lew D, Waldvogel F. Foreign body infections due to *Staphylococcus epidermidis*. Ann Med. 2009;41(2):109–19.
35. Uckay I, Buchs NC, Seghrouchni K, Assal M, Hoffmeyer P, Lew D, Bacterial Osteomylitis: The Clinician's Point of View. Diagnostic imaging of infections and inflammatory diseases: a multidisciplinary approach. 1st ed. Geneva: Wiley; 2014.
36. Uckay I, Assal M, Legout L, Rohner P, Stern R, Lew D, et al. Recurrent osteomyelitis caused by infection with different bacterial strains without obvious source of reinfection. J Clin Microbiol. 2006;44(3):1194–6.
37. Sendi P, Proctor RA. Staphylococcus aureus as an intracellular pathogen: the role of small colony variants. Trends Microbiol. 2009;17(2):54–8.
38. Brady RA, Leid JG, Costerton JW, Shirtliff ME. Osteomyelitis: clinical overview and mechanisms of infection persistence. Clinical Microbiol. 2006;28(9):65–72.
39. Kim PJ, Steinberg JS. Wound care: biofilm and its impact on the latest treatment modalities for ulcerations of the diabetic foot. Semin Vasc Surg. 2012;25(2):70–4.
40. Harrison-Balestra C, Cazzaniga AL, Davis SC, et al. A wound-isolated Pseudomonas aeruginosa grows a biofilm in vitro within 10 hours and is visualized by light microscopy. Dermatol Surg. 2003;29(6):631–5.
41. Thomsen TR, Aasholm MS, Rudkjobing VB, Saunders AM, Bjarnsholt T, Givskov M, et al. The bacteriology of chronic venous leg ulcer examined by culture-independent molecular methods. Wound Repair Regen. 2010;18(1):38–49.
42. Bariteau JT, Waryasz GR, McDonnell M, Fischer SA, Hayda RA, Born CT. Fungal osteomyelitis and septic arthritis. J Am Acad Orthop Surg. 2014;22(6):390–401.
43. Dirschl DR, Almekinders LC. Osteomyelitis: common causes and treatment recommendations. Drugs. 1993;45(1):29–43.
44. Vardakas KZ, Kontopidis I, Gkegkes ID, Rafailidis PI, Falagas ME. Incidence, characteristics, and outcomes of patients with bone and joint infections due to community-associated methicillin-resistant Staphylococcus aureus: a systematic review. Eur J Clin Microbiol Infect Dis. 2013;32(6):711–21.
45. Aragon-Sanchez J, Lipsky BA, Lazaro-Martinez JL. Diagnosing diabetic foot osteomyelitis: is the combination of probe-to-bone and plain radiography sufficient for high-risk patients? Diabet Med. 2011;28(2):191–4.
46. Acharya S, Soliman M, Egun A, Rajbhandari SM. Conservative management of diabetic foot osteomyelitis. Diabetes Res Clin Pract. 2013;101(3):e18–20.
47. Corey SV, Butterworth ML. Puncture wounds. In: Southerland JT, Boberg JS, Downey MS, Nakra A, Rabjohn LV, editors. McGlamry's comprehensive textbook of foot and ankle surgery. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2012.
48. Laughlin RT, Reeve F, Wright DG, Mader JT, Calhoun JH. Calcaneal osteomyelitis caused by nail puncture wounds. Foot Ankle Int. 1997;18(9):575–7.
49. Weber EJ. Plantar puncture wounds: a survey to determine the incidence of infection. J Accid Emerg Med. 1996;13(4):274–7.
50. Onwubalili JK. Sickle cell disease and infection. J Infect. 1983;7(1):2–20.
51. Zimmerli W, Trampuz A, Ochsner PE. Prosthetic joint infections. N Engl J Med. 2004;351:1645–54.
52. Liu DS, Sofiadellis F, Ashton M, MacGill K, Webb A. Early soft tissue coverage and negative pressure wound therapy optimizes patient outcomes in lower limb trauma. Injury. 2012;43(6):772–8.
53. Gopal S, Majumder S, Batchelor AG, Knight SL, De Boer P, Smith RM. Fix and flap: the radical orthopaedic and plastic treatment of severe open fractures of the tibia. J Bone Joint Surg. 2000;82(7):959–66.
54. Hou Z, Irqit K, Strohecker KA, Matzko ME, Wingert NC, DeSantis JG, Smith WR. Delayed flap reconstruction with vacuum-assisted closure management of the open IIIB tibial fractures. J Trauma. 2011;71(6):1705–8.
55. Pinckney LE, Currarino G, Kennedy LA. The stubbed great toe: a cause of occult compound fracture and infection. Radiology. 1981;138(2):375–7.
56. Böhm E, Josten C. What's new in exogenous osteomyelitis. Pathol Res Pract. 1992;188(1–2):254–8.
57. Jeffcoate WJ, Lipsky BA. Controversies in diagnosing and managing osteomyelitis of the foot in diabetes. Clin Infect Dis. 2004;39 Suppl 2:s115–22.
58. Boyko EJ, Ahroni JH, Stensel V, Forsberg RC, Davignon DR, Smith DG. A prospective study of risk factors for diabetic foot ulcer. Diabetes Care. 1999;22(7):1036–42.
59. Peters EJ, Lavery LA, Armstrong DG. Diabetic lower extremity infection influence of physical, psychological, and social factors. J Diabetes Complications. 2005;19(2):107–12.
60. Shilling AM, Raphael J. Diabetes, hyperglycemia, and infections. Best Pract Res Clin Anaesthesiol. 2008;22(3):519–35.
61. Janis JE, Kwon RK, Attinger CE. The new reconstructive ladder: modifications to the traditional model. Plast Reconstr Surg. 2011;127 Suppl 1:205S–12.
62. Iorio ML, Shuck J, Attinger CE. Wound healing in the upper and lower extremities: a systematic review on the use of acellular dermal matrices. Plast Reconstr Surg. 2012;130(5 Suppl 2):232S–41.
63. Parrett BM, Pomahac B, Demling RH, Orgill DP. Fourth degree burns to the lower extremity with exposed tendon and bone: a ten-year experience. J Burn Care Res. 2006;27(1):34–9.

64. Parrett BM, Matros E, Pribaz JJ, Orgill DP. Lower extremity trauma: trends in the management of soft tissue reconstruction of open tibia-fibula fractures. Plast Reconstr Surg. 2006;117(4): 1315–22.
65. Ofer N, Baumeister S, Ohlbauer M, Germann G, Saurbier M. Microsurgical reconstruction of the burned upper extremity. Handchir Mikrochir Plast Chir. 2005;37(4):245–55.
66. Baumeister S, Koller M, Dragu A, Germann G, Sauerbier M. Principles of microvascular reconstruction in burn and electrical burn injuries. Burns. 2005;31:92–8.
67. Teh J, Berendt T, Lipsky BA. Investigating suspected bone infection in the diabetic foot. BMJ. 2009;339:b4690.
68. Lavery LA, Armstrong DG, Peters EJ, Lipsky BA. Probe-to-bone test for diagnosing diabetic foot osteomyelitis: reliable or relic? Diabetes Care. 2007;30:270–4.
69. Shone A, Burnside J, Chipchase S, Game F, Jeffcoate W. Probing the validity of the probe-to-bone test in the diagnosis of osteomyelitis of the foot in diabetes. Diabetes Care. 2006;29(4):945.
70. 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(4):519–27.
71. Capriotti G, Chianelli M, Signore A. Nuclear medicine imaging of diabetic foot infection: results of meta-analysis. Nucl Med Commun. 2006;27(10):757–64.
72. Sanverti SE, Ergen FB, Oznur A. Current challenges in imaging of the diabetic foot. Diabet Foot Ankle. 2012;3:5. http://dx.doi.org/10.3402/dfa.v3i0.18754.
73. Morrison WB, Schweitzer ME, Batte WG, Radack DP, Russel KM. Osteomyelitis of the foot: relative importance of primary and secondary MR imaging signs. Radiology. 1998;207(3):625–32.
74. Collins MS, Schaar MM, Wenger DE, Mandrekar JN. T1-weighted MRI characteristics of pedal osteomyelitis. AJR Am J Roentgenol. 2005;185(2):386–93.
75. Rozzanigo U, Tagliani A, Vittorini E, Pacchioni R, Brivio LR, Caudana R. Role of magnetic resonance imaging in the evaluation of diabetic foot with suspected osteomyelitis. Radiol Med. 2009;114(1):121–32.
76. Gnanasegaran G, Chicklore S, Vijayanathan S, O'Doherty MJ, Fogelman I. Diabetes and bone: advantages and limitations of radiological, radionuclide and hybrid techniques in the assessment of diabetic foot. Minerva Endocrinol. 2009;34(3):237–54.
77. Donovan A, Schweitzer ME. Current concepts in imaging diabetic pedal osteomyelitis. Radiol Clin North Am. 2008;46(6):1105–24.
78. Russell JM, Peterson JJ, Bancroft LW. MR imaging of the diabetic foot. Magn Reson Imaging Clin N Am. 2008;16(1):59–70.
79. Ahmadi ME, Morrison WB, Carrino JA, Schweitzer ME, Raikin SM, Ledermann HP. Neuropathic arthropathy of the foot with and without superimposed osteomyelitis: MR imaging characteristics. Radiology. 2006;238(2):622–31.
80. Meyr AJ, Singh S, Zhang X, Khilko N, Mukherjee A, Sheridan MJ, Khurana JS. Statistical reliability of bone biopsy for the diagnosis of diabetic foot osteomyelitis. J Foot Ankle Surg. 2011;50(6): 663–7.
81. Petrosillo N. Epidemiology of infections in the new century. In: Signore A, Quintero AM, editors. Diagnostic imaging of infections and inflammatory disease: a multidisciplinary approach. 1st ed. Hoboken: Wiley; 2014.
82. Lipsky BA. Osteomyelitis of the foot in diabetic patients. Clin Infect Dis. 1997;25(6):1318–26.
83. Kaleta JL, Fleischli JW, Reilly CH. The diagnosis of osteomyelitis in diabetes using erythrocyte sedimentation rate:a pilot study. J Am Podiatr Med Assoc. 2001;91(9):445–50.
84. Upchurch Jr GR, Keagy BA, Johnson Jr G. An acute phase reaction in diabetic patients with foot ulcers. Cardiovasc Surg. 1997;5(1):32–6.
85. Bencardino JT, Restrepo-Velez Z, Bujan R, Jaramillo D. Radiological Imaging of osteomyelitis. In: Signore A, Quintero AM, editors. Diagnostic imaging of infections and inflammatory disease: a multidisciplinary approach. 1st ed. New Jersey: Wiley & Sons; 2014. p. 29–53.
86. Lesens O, Desbiez F, Vidal M, Robin F, Descamps S, Beytout J, et al. Culture of per-wound bone specimen: a simplified approach for the medical management of diabetic foot osteomyelitis. Clin Microbiol Infect. 2011;17(2):1469–691.
87. Senneville E, Melliez H, Beltrand E, Legout L, Valette M, Cazaubiel M, et al. Culture of percutaneous bone biopsy specimens for diagnosis of diabetic foot osteomyelitis: concordance with ulcer swab cultures. Clin Infect Dis. 2006;42(1): 57–62.
88. Centers for Disease Control and Prevention. National diabetes fact sheet: national estimates and general information on diabetes and prediabetes in the United States, 2011. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention; 2011.
89. Berendt AR, Peters EJ, Bakker PK, Embil JM, Eneroth M, Hinchliffe RJ, et al. Diabetic foot osteomyelitis: a progress report on diagnosis and a systematic review of treatment. Diabetes Metab Res Rev. 2008;24 Suppl 1:S145–61.
90. Lazaro-Martinez JL, Aragon-Sanchez J, Garcia-Morales E. Antibiotics versus conservative surgery for treating diabetic foot osteomyelitis: a randomized comparative trial. Diabetes Care. 2014;37:789–95.
91. Mouzopoulos G, Kanakaris NK, Kontakis G, Obakponovwe O, Townsend R, Giannoudis PV. Management of bone infections in adults: the surgeon's and microbiologist's perspectives. Injury. 2011;42 Suppl 5:S18–23.
92. Zaoutis T, Localio AR, Leckerman K, Saddlemire S, Bertoch D, Keren R. Prolonged intravenous therapy versus oral antimicrobial therapy for acute osteomyelitis in children. Pediatrics. 2009;123(2):636–42.
93. Conterno LO, Turchi MD. Antibiotics for treating chronic osteomyelitis in adults. Cochrane Database Syst Rev [Internet]. 2013 Sep [cited 2014 Aug 7]. http://onlinelibrary.wiley.com.libproxy.temple. edu/doi/10.1002/14651858.CD004439.pub3/abstract.
94. Carek PJ, Dickerson LM, Sack JL. Diagnosis and management of osteomyelitis. Am Fam Physician. 2001;63(12):2413–20.
95. Henke PK, Blackburn SA, Wainess RW, Cowan J, Terando A, Proctor M, et al. Osteomyelitis of the foot and toe in adults is a surgical disease. Ann Surg. 2005;241(6):885–94.
96. Simpson AH, Deakin M, Latham JM. Chronic osteomyelitis. The effect of the extent of surgical resection on infection-free survival. J Bone Joint Surg Br. 2001;83(3):403–7.
97. Eckardt JJ, Wirganowicz PZ, Mar T. An aggressive surgical approach to the management of chronic osteomyelitis. Clin Orthop Relat Res. 1994;298:229–39.
98. Melamed EA, Peled E. Antibiotic impregnated cement spacer for salvage of diabetic osteomyelitis. Foot Ankle Int. 2012;33(3):213–9.
99. Roukis TS, Landsman AS. Salvage of the first ray in a diabetic patient with osteomyelitis. J Am Podiatr Med Assoc. 2004;94(5): 492–8.
100. Schweinberger MH, Roukis TS. Salvage of the first ray with external fixation in the high-risk patient. Foot Ankle Spec. 2008;1(4):210–3.
101. Londahl M. Hyperbaric oxygen therapy as adjunctive treatment for diabetic foot ulcers. Int J Low Extrem Wounds. 2013;12(2):152–7.
102. Londahl M, Katzman P, Nilsson A, Hammarlund C. Hyperbaric oxygen therapy facilitates healing of chronic foot ulcers in patients with diabetes. Diabetes Care. 2010;33(5):998–1003.

103. Davis JC, Heckman JD, DeLee JC, Buckwold FJ. Chronic non-hematogenous osteomyelitis treated with adjunctive hyperbaric oxygen therapy. J Bone Joint Surg Am. 1986;68(8):1210–7.
104. Estherhai Jr JL, Pisarello J, Brighton CT, Heppenstall RB, Gellman H, Goldstein G. Adjunctive hyperbaric oxygen therapy in the treatment of chronic refractory osteomyelitis. J Trauma. 1987;27(7):763–8.
105. Fang RC, Galiano RD. Adjunctive therapies in the treatment of osteomyelitis. Semin Plast Surg. 2009;23(2):141–7.
106. Margolis DJ, Gupta J, Hoffstad O, Papdopoulos M, Glick HA, Thom SR, et al. Lack of effectiveness of hyperbaric oxygen therapy for the treatment of diabetic foot ulcer and the prevention of amputation: a cohort study. Diabetes Care. 2013;36(7):1961–6.
107. Kranke P, Bennett MH, Martyn-St James M, Schnabel A, Debus SE. Hyperbaric oxygen therapy for chronic wounds. Cochrane Database Syst Rev. 2012;18(4), CD004123.
108. Gentry LO, Rodriguez-Gomez G. Ofloxacin versus parenteral therapy for chronic osteomyelitis. Antimicrob Agents Chemother. 1991;35(3):538–41.
109. Stengel D, Bauwens K, Sehouli J, Ekkernkamp A, Porzsolt F. Systematic review and meta-analysis of antibiotic therapy for bone and joint infections. Lancet Infect Dis. 2001;1(3): 175–88.
110. Snyder RJ, Cohen MM, Sun C, Livingston J. Osteomyelitis in the diabetic patient: diagnosis and treatment. Part 2: medical, surgical, and alternative treatments. Ostomy Wound Manage. 2001;47(3): 24–30. 3.
111. Widatalla AH, Mahadi SEI, Shawer MA, Mahmoud SM, Abdelmageed AE, Ahmed ME. Diabetic foot infections with osteomyelitis: efficacy of combined surgical and medical treatment. Diabet Foot Ankle. 2012;3:18809–15. http://diabeticfootandankle.net/index. php/dfa/article/view/18809.
112. Akarsus S, Tekin L, Safaz I, Goktepe AS, Yazicioglu K. Quality of life and functionality after lower limb amputations: comparison between uni- vs bilateral amputee patients. Prosthet Orthot Int. 2013;37(1):9–13.
113. Boutoille D, Feraille A, Maulaz D, Krempf M. Quality of life with diabetes-associated foot complications: comparison between lower-limb amputation and chronic foot ulceration. Foot Ankle Int. 2008;29(11):1074–8.
114. Deans SA, McFadyen AK, Rowe PJ. Physical activity and quality of like: a study of a lower-limb amputee population. Prosthet Orthot Int. 2008;32(2):186–200.
115. Asano M, Rushton P, Miller WC, Deathe BA. Predictors of quality of life among individuals who have a lower limb amputation. Prosthet Orthot Int. 2008;32(2):231–43.
116. Horgan O, MacLachlan M. Psychosocial adjustment to lower-limb amputation: a review. Disabil Rehabil. 2004;26(14–15):837–50.
117. Toursarkissian B, Shireman PK, Harrison A, D'Ayala M, SchoolField J, Sykes MT. Major lower-extremity amputation: contemporary experience in a single Veterans Affairs institution. Am Surg. 2002;68(7):606–10.
118. Evans KK, Attinger CE, Al-Attar A, Salgado C, Chu CK, Mardini S, Neville R. The importance of limb preservation in the diabetic population. J Diabetes Complications. 2011;25(4):227–31.
119. Tice AD, Hoaglund PA, Shoultz DA. Outcomes of osteomyelitis among patients treated with outpatient parenteral antimicrobial therapy. Am J Med. 2003;114(9):723–8.
120. Mader JT, Calhoun JH, Lazzarini L. Adult long bone osteomyelitis. In: Calhoun JH, Mader JT, editors. Musculoskeletal infections. New York: Marcel Dekker; 2003. p. 133–64.
121. Buckholtz JM. The surgical management of osteomyelitis: with special reference to a surgical classification. J Foot Surg. 1987;26 Suppl 1:s17–24.