Osteomyelitis of the Foot and Ankle

Diagnosis, Epidemiology, and Treatment

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KEYWORDS

• Osteomyelitis • Diabetic foot • Imaging • Surgical treatment • Laboratory studies • Adjuvant therapies

KEY POINTS

- Osteomyelitis of the foot and ankle is a common, potentially devastating condition with diagnostic and treatment challenges.
- History and physical examination, laboratory studies, vascular studies, histologic and microbiologic analyses, and various imaging modalities contribute to the diagnosis and treatment.
- Treatment should take a multidisciplinary approach to optimize patient factors, ensure eradication of the infection, and restore function.
- Surgical treatment needs to consider the physiology of the infection and the patient, must be extensive, and may use multiple techniques to achieve successful outcomes.
- Adjuvant therapies and novel laboratory markers may enhance outcomes as they are further studied and used.

INTRODUCTION

Osteomyelitis of the foot and ankle can be extremely debilitating to patients and a management challenge to the orthopedic surgeon. In the preantibiotic era, acute staphylococcal osteomyelitis carried a mortality rate of 50%.[1] Osteomyelitis of the foot and ankle can arise from multiple etiologies, and one of the most frequently encountered clinical scenarios is in the context of diabetic foot infections. The incidence of diabetic

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foot infections is 36.5 per 1000 persons per year, with a lifetime incidence of patients with diabetes developing a diabetic foot ulcer of 25%.[2–5] Underlying osteomyelitis is present in 20% to 68% of diabetic foot ulcers.[6–9] The presence of osteomyelitis in diabetic foot infections has an amputation rate of up to 66%.[9,10] In-hospital mortality associated with osteomyelitis in one study was 1.6%.[11] The economic burden of osteomyelitis is severe, with a median length of stay of 7 hospital days, mean hospital charges $19,000, and the direct costs of amputation associated with osteomyelitis exceeding $34,000.[2,3,11] Understanding how to accurately diagnose and effectively treat osteomyelitis is critical for the foot and ankle surgeon.

CLASSIFICATION AND PATHOPHYSIOLOGY OF OSTEOMYELITIS

Several classifications of osteomyelitis and diabetic foot wounds exist. Classification of osteomyelitis popularized by Waldvogel focused on the duration and mechanism of infection.[12] The duration of osteomyelitis is classified as acute, subacute, or chronic. Acute osteomyelitis refers to inflammatory bone changes caused by pathogens with symptoms manifesting within 2 weeks of infection.[12,13] Histologic findings of acute osteomyelitis include microorganisms, neutrophil infiltration, and congested or thrombosed nutrient blood vessels.[10,14] Chronic osteomyelitis is defined by the presence of necrotic bone and the absence of osteocytes, and symptoms may not occur until 6 weeks of infection.[10,12–14] Mechanisms of infection in osteomyelitis include hematogenous or exogenous spread. Hematogenous osteomyelitis involves bacteremia and seeding of the bone with an organism from a remote source.[12] Hematogenous osteomyelitis is primarily seen in pediatric patients, patients with chronic indwelling catheters, and intravenous drug abusers.[15] It generally occurs in bones with rich blood supply, such as the metaphases of long bones in children and the vertebral bodies of adults.[12,16] Exogenous osteomyelitis occurs from direct inoculation of the bone caused by contiguous spread from adjacent tissue, open fractures, penetrating trauma, or iatrogenic postsurgical contamination.[12,15,16] In diabetic foot osteomyelitis, there typically is contiguous spread from adjacent soft tissue infection or ulcer.

The pathophysiology of osteomyelitis begins as the infection spreads through the periosteum or is seeded hematogenously and extends within the medullary canal. The increased intramedullary pressure secondary to inflammation leads to bone necrosis and the overlying periosteal reaction begins the formation of new bone, creating an involucrum.[1] Inflammatory factors and leukocytes further contribute to bone necrosis and destruction. Local vascular channels are compressed and obliterated by the inflammatory process, creating areas of necrosis and sequestra where antibiotic penetration is insufficient.[1] At the edge of the infarcted microvascular channels, there is relative hyperemia, which causes bone dissolution and localized osteoporosis secondary to increased osteoclastic activity.[1] Osteoclastic activity is further stimulated by inflammatory factors, such as interleukin (IL)-1 and tumor necrosis factor released by inflammatory cells in response to bacterial antigens, leading to further attempts at remodeling because of dissolution.[6]

The Cierny classification of chronic osteomyelitis uses the anatomic location and extent of infection and also considers the physiologic factors of the patient.[17] There are four anatomic types: medullary (I), superficial (II), localized (III), and diffuse (IV). Based on the comorbidities and clinical status of the patient, the physiologic class of the host is defined as normal (A host), compromised (B host), or prohibitive (C host). This classification is presented in **Table 1**.

Consideration of surrounding soft tissues or staging of diabetic foot wounds is also important in foot and ankle osteomyelitis. The Wagner classification of diabetic foot

Table 1
Cierny and Mader system for chronic osteomyelitis

Anatomic type		
I	Medullary	Nidus is medullary; endosteal disease
II	Superficial	Infection limited to cortical surface infected because of coverage defect
III	Localized	Localized infection involving a stable, well-demarcated lesion with full-thickness cortical sequestration and cavitation Complete excision/debridement does NOT lead to instability
IV	Diffuse	Diffuse osteomyelitic lesion with mechanical instability that requires complex reconstruction
Physiologic class		
A host	Normal	Immunocompetent with good local vascularity; will have normal immune response to infection and healing response to surgery
B host	Compromised	Local or systemic factors that compromise immunity or healing potential
C host	Prohibitive	Results of treatment are potentially more damaging than the presenting condition

wounds consists of six grades: high-risk foot without ulcer (grade 0), superficial noninfected ulcer (grade 1), deep infected ulcer with limited cellulitis (grade 2), very deep infected ulcer with tendon/fascial and/or bone involvement (grade 3), limited gangrene (grade 4), or extensive gangrene and tissue necrosis (grade 5).[18] This classification is presented in **Table 2**.

EPIDEMIOLOGY

Many cases (11%–55%) of osteomyelitis in diabetic foot infections are polymicrobial, with an average of 2.3 organisms isolated per patient.[19–22] The most frequently isolated organism in osteomyelitis is *Staphylococcus aureus* (up to 49.2% of cases).[21,23] *S aureus* adheres to multiple components of the bone matrix, including fibrinogen, fibronectin, laminin, bone sialoglycoprotein, and clumping factor A via bacterial surface protein adhesins known as microbial surface components recognizing adhesive matrix molecules.[1,16,24,25] *S aureus* also has several mechanisms to resist host defenses. Staphylococcal protein A is expressed on the cell wall and binds to IgG via Fc-reactive sites, defending against phagocytosis.[1] The surface proteins of *S aureus* induce the release of tumor necrosis factor-α, prostaglandins, and IL-1 from immune

Table 2
Wagner classification of diabetic foot wounds

Wagner Grade 0	Wagner Grade 1	Wagner Grade 2	Wagner Grade 3	Wagner Grade 4	Wagner Grade 5
High-risk foot, no ulcerations	Superficial, noninfected ulcer	Deep, infected ulcer Limited cellulitis	Deep, infected ulcer with tendon, fascia, and/or bone involvement	Limited gangrene	Extensive gangrene

cells, which increase osteoclast activity and cause osteolysis.[6,26] *S aureus* forms a polysaccharide pseudocapsule "biofilm" that further secures it to bone or surgical implants and interferes with opsonization, phagocytosis, and antibiotic penetration.[1,25] *Staphylococcus epidermidis*, group A streptococcus, and *Pseudomonas aeroginosa* can also form biofilms in osteomyelitis.[1]

Methicillin-resistant *S aureus* (MRSA) prevalence is increasing and accounts for 15.3% of osteomyelitis in diabetic foot infections.[23,27] MRSA and other multidrug-resistant organism infections are more common in institutionalized patients or patients with a history of recurrent or recent hospitalization.[28] MRSA infections are associated with a higher body temperature and white blood cell count than methicillin-sensitive *S aureus* osteomyelitic infections.[29] Patients with MRSA osteomyelitis of the foot and ankle have been shown to undergo a greater number of surgical procedures to achieve eradication of the infection, but there is not a statistically significant difference in amputation rate or healing time when early aggressive treatment is initiated between MRSA and methicillin-sensitive *S aureus* osteomyelitis.[6,28–30] The rise in prevalence of MRSA infections has prompted many clinicians to include empirical broad-spectrum antibiotic treatment as part of early, aggressive treatment and later tailor antibiotic therapy according to culture and sensitivity data.[29,30]

P aeruginosa is isolated in 2.5% to 14.6% of foot osteomyelitic infections.[21,23] *Pseudomonas* is a common infecting organism in hematogenous osteomyelitis associated with intravenous drug abuse.[31] A history of a puncture wound to the foot is another common etiologic factor in *Pseudomonas* osteomyelitis.[23] *P aeruginosa* osteomyelitis of the foot is associated with a significantly higher recurrence rate and more strongly correlated with amputation than *S aureus* osteomyelitis.[32]

Other common organisms include gram-negative bacteria (7.0%–33.7%), *Streptococcus* (15.4%), coliforms (8.5%), and anaerobes (11.5%).[21,23] Enterobacteriacae are the most common gram-negative bacteria isolated.[21] *Enterococcus* is a gram-positive bacteria commonly found in patients who have received prior treatment with cephalosporins, because *Enterococcus* has inherent resistance to these antibiotics.[21,22] Group B streptococcus is the most likely organism in otherwise healthy 2- to 4-week old infants with osteomyelitis and is also a common contaminant in patients with a history of skin ulceration or surgery.[31] Fungal infections are seen in patients receiving prolonged intravenous therapy or parental nutrition for chronic illnesses.[31,33] These are often attributed to specimen contamination, but fungal osteomyelitis is a real entity and must be addressed if identified because of difficulty with complete eradication. Anaerobic infections are more likely to be present in cases of infections that are severe, long-standing, resistant to antibiotic therapy, and accompanied by foul odor and necrotic tissue debris.[21,34] *Salmonella* is a common organism in osteomylitic infections in patients with sickle cell or sickle trait hemoglobinopathies.[31]

DIAGNOSING OSTEOMYELITIS

History and Physical Examination

The history and physical examination can be very informative when approaching suspected osteomyelitis. Pertinent historical information includes the timing, duration, nature, and quality of symptoms, such as swelling, fevers, chills, myalgias, diaphoresis, drainage, pain, and redness.[1] Symptoms are often vague, highly variable, and lack specificity when used in isolation. History of trauma, travel, or environmental exposures is essential. A comprehensive past medical history should focus on current or chronic illnesses, the history and management of comorbid conditions, surgical

history, functional and ambulatory status, age, overall health, and nutritional status. In diabetic patients, the duration of disease, current and past medications, history of glycemic control, and presence of microvascular or macrovascular complications, especially neuropathy or peripheral vascular disease, should be documented.[1,4,13] Factors significantly associated with the presence of osteomyelitis include increased duration of diabetes, history of previous foot ulcer, prior lower-extremity amputation, lower-extremity vascular procedure, Charcot-type foot fracture, or history of recurrent foot infections.[5]

On physical examination, it is important to note any contractures, foot deformities, or gait abnormalities. The Silfverskiöld knee flexion test is used to distinguish between isolated gastrocnemius contracture and combined shortening of the gastrocnemius-soleus complex in nonspastic contracture by measuring the range of ankle dorsiflexion with the knee flexed and the knee straight.[35] Increased dorsiflexion with the knee flexed indicates isolated gastrocnemius contracture. Semmes-Weinstein monofilament testing with a 4.5-g should be performed to evaluate for neuropathy.[36] Examination and documentation of the vascular status of the extremity, including pulses, skin, and presence or absence of swelling, is critical.[6] The presence and location of skin callouses on the foot should be noted because these indicate sites of pressure. In a nonneuropathic foot, pressure most commonly occurs in the plantar forefoot at the metatarsal heads, especially the first and second toes or the fifth metatarsophalangeal joint.[10,14] Accordingly, the metatarsal heads are the most common location of osteomyelitis in diabetic feet.[6] In neuropathic feet, callous can also predominate over the posterior plantar calcaneus.[10,14] In neuropathic feet with mid-foot prominence and a rocker-bottom foot deformity, callous is most prominent under the cuboid.[10] Local signs of inflammation including the classic redness (rubor), tenderness (dolor), heat (calor), and swelling (tumor) all alert the clinician to maintain a high suspicion for infection.[1] In delineating erythema secondary to neuro-osteoarthropathy, the erythema tends to be dependent and resolve with elevation of the extremity, whereas the erythema is less likely to resolve with elevation in cases of infection.[6] One highly suggestive clinical finding of pedal osteomyelitis is the "sausage toe" deformity: the toe is swollen and erythematous with obliteration of the normal toe contour in addition to a local ulceration of the toe or adjacent metatarsophalangeal joint.[10,37]

Documentation of the size, depth, location, drainage, and a detailed probe examination should be included when an ulcer or sinus tract is present. A greater than 2 cm^2 diabetic foot ulcer has a sensitivity of 56% and specificity of 92% in diagnosing underlying osteomyelitis.[8] Ulcer depth greater than 3 mm is also highly suggestive of underlying osteomyelitis, with a univariate odds ratio (OR) of 10.4.[3] The "probe-to-bone" test is performed at bedside and has a sensitivity of 56% to 66%, specificity of 85% to 92%, positive predictive value of 89%, and OR 5.0 in the diagnosis of osteomyelitis.[3,7,38–40] The "probe-to-bone" test is performed by probing the wound with a sterile, blunt, stainless steel probe; a positive test is indicated if a hard, gritty structure (bone) is encountered.[7] Exposed bone has a positive likelihood ratio (LR) of 9.2 for osteomyelitis in diabetic foot wounds.[3] One study calculated the pooled diagnostic OR for exposed bone or a positive probe-to-bone test to be 49.45, indicating that these tests when positive have excellent power to determine the presence of osteomyelitis.[40]

Laboratory Studies

Laboratory markers are useful in diagnosis and trending therapeutic efficacy in osteomyelitis. A complete blood cell count with differential is indicated in patients with a

suspected infection or inflammatory conditions. White blood cell count greater than 11.0 $\times$ $10^3/\mu L$ (OR, 6.3) and a neutrophil percentage greater than 70% (OR, 3.8) are suggestive of osteomyelitis.[3] The white blood cell count may be normal, however, and is only elevated in 35% of patients.[4,41,42] A basic or comprehensive metabolic panel contains useful markers of the physiologic status of the patient. The calcium, phosphorus, and alkaline phosphatase levels are elevated in malignancy and metabolic disorders, whereas they are normal in osteomyelitis.[43] The nutritional status can be assessed on values of serum proteins (malnutrition is defined as albumin <3.5 mg/dL; prealbumin <15 mg/dL; transferrin <200 mg/dL), nitrogen balance, cholesterol, and creatinine.[44] The measure of glycosylated hemoglobin (HbA_{1c}) is a useful marker of compliance and glucose control in diabetic patients. Patients with higher HbA_{1c} values have longer healing times and higher rates of amputation in patients with lower-extremity ulcers and osteomyelitis.[40,45,46]

The erythrocyte sedimentation rate (ESR) is a marker of inflammation that is elevated in osteomyelitis within 24 hours of the onset of symptoms, returning to normal after 3 to 4 weeks of adequate treatment.[25] An ESR of greater than or equal to 70 mm/h has a sensitivity of 89%, specificity of 100%, and positive LR of 11 (95% confidence interval, 1.6–79.0), making it highly suggestive of osteomyelitis.[3,39,47] In 70% of cases with osteomyelitis, however, the ESR is less than 70 mm/h.[10] An ESR less than 70 has a summary LR of 0.34 (95% confidence interval, 0.06–1.90).[39] ESR greater than 60 mm/h in addition to clinical indicators (ulcer depth >3 mm) has an accuracy of 88% in the prediction of osteomyelitis.[3]

C-reactive protein (CRP) is a measure of the acute phase response to inflammation and is highly sensitive in the diagnosis of osteomyelitis. CRP is elevated within 6 hours of onset of symptoms, peaks within 48 hours of infection, and begins to normalize within 1 week of disease resolution.[25] CRP greater than 3.2 mg/dL has a sensitivity of 85%, specificity of 77%, negative LR of -0.23, OR of 10.8, and accuracy of 88%.[3] The CRP normalizes more rapidly than the ESR value; both should be monitored weekly to monitor the course of treatment in osteomyelitis.[25]

Novel markers of bone turnover are being investigated, and may have utility in the diagnosis and monitoring of treatment of patients with osteomyelitis. One study compared two such markers, serum amino-terminal telopeptides and bone alkaline phosphatase, in patients with diabetes with and without osteomyelitis but failed to note a difference.[48] Other antimicrobial peptides and biomarkers, such as IL-1 and IL-6, are being studied in orthopedic periprosthetic joint infections, and may have further utility in osteomyelitis.[49] Further investigation is required to determine the clinical application of such tests.

Imaging Modalities

Plain radiographs are an appropriate and indicated first step in the evaluation of a patient with suspected osteomyelitis. Initial radiographs may be negative or show only soft tissue swelling, which typically develops 1 to 3 days after the onset of infection. The radiographic signs of osteomyelitis include periosteal reaction, sequestra, loss of trabecular pattern, or cortical destruction and typically are not seen until 10 to 14 days after the onset of infection.[6,16,50–52] Bone mineral loss of 30% to 50% is required before positive radiographic findings are evident on plain radiographs.[51,53–55] Therefore, radiographs should be repeated within 2 to 4 weeks when clinical suspicion of osteomyelitis persists.[4,10,56] In addition, plain radiographs provide valuable information on foot alignment, joint congruency, and bony architecture. In chronic osteomyelitis with a draining sinus tract, sinography performed by injecting radiopaque liquid into the sinus tract can aid in localizing the focus of infection.[53]

Computed tomography (CT) provides excellent definition of cortical bone. Because of this, it is extremely useful in identifying sequestra, periosteal reaction, extent of bony erosion, and cortical destruction.[53,57] CT also visualizes small foci of gas within the medullary canal, foreign bodies, soft tissue changes, and the full extent of sinus tracts.[57] When MRI is unavailable because of patient factors or contraindications, CT is the study of choice to localize osteomyelitis.[57]

Nuclear medicine studies are useful in the diagnosis of osteomyelitis.[58–60] Three-phase technetium-99m methylene diphosphate (MDP) bone scan can confirm the diagnosis of osteomyelitis within 24 to 48 hours of onset.[53,61] A normal three-phase Tc-99m MDP bone scan nearly entirely excludes the diagnosis of osteomyelitis.[55,62] Three-phase bone scintigraphy uses a radiotracer and images at three phases: (1) nuclear angiogram/blood flow phase (immediately after injection), (2) blood pool phase (within 5 minutes of injection), and (3) a bone phase (3 hours after injection).[63] Cellulitis is characterized by high uptake in the blood flow and blood pool phases, with normal intake in the bone phase. In contrast, osteomyelitis has increasing uptake over all three phases throughout the course of the study.[63] The pooled sensitivity and specificity for three-phase bone study is 81% and 28%, respectively, with a diagnostic OR of 2.10 and summary measure of accuracy (Q*) of 0.60.[40] The limited specificity is caused by the uptake of the radiotracer at all sites of bone metabolism, irrespective of the underlying cause.[64] In patients with early high uptake intensity, further delayed images are not needed to make an accurate diagnosis of osteomyelitis.[10] In patients with early, mild uptake intensity, many advocate the addition of a fourth phase at 24 hours because this increases the overall accuracy of the test from 80% to 85%.[10,55,65]

Gallium scan is slightly more specific than bone scanning, but false-positives can occur in areas of bone healing, neuropathic fractures, neoplasm, or noninfected prostheses.[1,66] Gallium scans use gallium-67 citrate, which binds to acute phase reactants, such as transferrin and lactoferrin as they travel in the bloodstream to areas of infection where the metabolism of iron by bacteria, chemotaxis, and uptake by leukocytes cause focal accumulation of the isotope.[1,51] Imaging is performed 24 hours after the injection of the isotope.[1] Normal gallium scan virtually excludes the presence of osteomyelitis and can be useful as a follow-up examination postoperatively to confirm eradication of the focus of osteomyelitis.[31] The reported sensitivity ranges from 25% to 80% with a specificity of 67% for gallium-67 scans.[1]

Indium-111–labeled leukocyte scans are extremely useful in differentiating acute osteomyelitis from neuro-osteoarthropathy in the diabetic foot.[31,51] Indium-111–labeled leukocytes accumulate at the site of infection by chemotaxis, then cross capillary walls (diapedesis). Leukocyte scans have a high sensitivity and specificity even in the face of coexisting fractures, adjacent cellulitis, and neuro-osteoarthropathy.[51] Chronic infections are not well imaged with indium-111, because the labeled leukocyte preparation consists primarily of neutrophils, whereas monocytes and lymphocytes predominate in chronic infection.[4,67] Leukocyte scans have a reported sensitivity of 89%, diagnostic OR of 10.7, and Q* of 0.59.[40] Combining Tc-99m MDP and indium-111 increases the ability to detect osteomyelitis, with a 100% sensitivity and 89% specificity reported.[4] This combination is useful, because the Tc-99m MDP scan localizes the anatomic site of infection and the indium-111 labels the infected bone.[68] Indium-111–labeled leukocyte scan combined with Tc-99m MDP scintigraphy is the imaging of choice in posttraumatic and nonunion site osteomyelitic infections.[64,69]

Fluorodeoxyglucose-labeled positron emission tomography (FDG-PET) uses 18-FDG, a marker of increased intracellular glucose metabolism, and monitors its

accumulation in areas of inflammation and infection.[57,70] FDG-PET has the highest accuracy of confirming or excluding the diagnosis of chronic osteomyelitis, with a pooled sensitivity of 96% and specificity of 91%.[66,67,71] Standardized uptake values in regions of sterile neuro-osteoarthropathy tend to be lower (0.7–2.4) and located in the midfoot, whereas the standardized uptake values associated with osteomyelitis are higher (2.9–6.2) and more likely located in the forefoot or calcaneus.[72] In cases with equivocal MRI findings or adjacent metal hardware complicating imaging, FDG-PET is a useful adjuvant.[64,67] FDG-PET alone has low spatial resolution compared with other imaging modalities, but this is easily overcome to achieve excellent anatomic detail and localization with the combined FDG-PET/CT study.[64,67,72]

Magnetic resonance imaging (MRI) is considered to be the imaging study of choice for the diagnosis and treatment of osteomyelitis.[50,57,67,73,74] MRI is useful in detecting intraosseous and subperiosteal abscesses, provides clear anatomic detail, does not expose the patient to ionizing radiation, and is rapidly completed and readily available in most centers.[31,75] The addition of gadolinium contrast improves the result and gives better anatomic detail of soft tissue involvement.[57] In acute osteomyelitis, the diagnosis on MRI is made based on altered bone marrow signal and signs of edema and inflammation in adjacent soft tissues. In chronic osteomyelitis, MRI may demonstrate a well-defined rim of high signal intensity surrounding a focus of active disease, known as the "rim sign."[57] On T1-weighted images, bone marrow becomes low signal intensity in acute osteomyelitis because there is a loss of fat in the bone marrow.[6,57] T2 and short-tau inversion recovery images demonstrate high signal intensity in the bone marrow, sinus tracts, and areas of soft tissue inflammation and cellulitis.[6,14,76] Osseous extent is best determined on T1 images, because T2 images can overestimate the amount of infected bone in preoperative planning.[14,77] Both osteomyelitis and bone marrow edema have high signal on T2 and short-tau inversion recovery MRI images; bone marrow edema has a normal T1 image, whereas osteomyelitis has a low signal density.[14,78] Soft tissue abscesses demonstrate low to intermediate signal on T1-weighted images and high signal on T2 images.[14] The pooled sensitivity of MRI in the diagnosis of osteomyelitis is 90%, specificity 79%, and diagnostic OR of 24.36, indicating excellent discriminatory power.[40] An overview of imaging studies useful in the diagnosis and treatment of osteomyelitis is found in **Table 3**.

Perfusion Studies

Arterial perfusion is an important clinical parameter to consider in the evaluation and treatment of osteomyelitis. Peripheral vascular disease contributes to ulceration and impaired wound healing, and decreases the ability to fight infection by disrupting the delivery of immune cells, oxygen, nutrients, and antibiotics to the affected extremity.[79] Diabetic peripheral vascular disease preferentially affects the tibial and peroneal arteries, and also the microvascular system.[79] Other risk factors for peripheral vascular disease include a positive family history, hypertension, tobacco use, hyperlipidemia, obesity, and hyperhomocystinemia.[79] Ankle brachial index is a noninvasive test that can be a useful objective measure of limb perfusion. A systolic ankle pressure of less than 50 mm Hg or ankle brachial index less than 0.6 suggests critical limb ischemia.[79] An absolute toe pressure of less than 30 mm Hg is considered inadequate for wound healing.[79,80] Ankle brachial index can be falsely elevated because of medial arterial calcinosis.[4,79] Another minimally invasive perfusion study is the arterial Doppler waveform or pulse volume recordings. Normal arterial waveforms are triphasic with good amplitude, reflective of the elasticity and recoil of healthy arterial wall musculature. Hemodynamically significant calcinosis or stenosis is demonstrated by blunting of the amplitude and biphasic or monophasic waveforms on the pulse volume

recordings.[79] Transcutaneous oxygen tension is another minimally invasive test to quantify tissue ischemia. Normal transcutaneous oxygen tension is defined as greater than or equal to 55 mm Hg. Tension of 30 mm Hg or greater suggests the arterial blood supply may be adequate for healing; less than 30 mm Hg prompts further vascular studies and possibly vascular interventions because wound healing is questionable.[4,79]

Arteriography is the gold standard for defining the anatomic location and extent of atherosclerotic occlusive disease of the lower extremities.[79] Angiography, although invasive, may allow for diagnosis and endovascular interventions, such as balloon angioplasty and stenting, in one procedure for the patient.[38] In patients with contraindications (especially renal) to angiography, MR angiography may be a useful alternative.[79]

Microbiology Studies

The gold standard diagnostic test for osteomyelitis is to obtain a biopsy specimen for histologic and microbiologic evaluation.[1,4,5,20,81] Culture and sensitivity data establish a definitive diagnosis and are invaluable in implementing an appropriate antibiotic regimen. Samples taken from an ulcer or sinus tract drainage are not sufficient to identify and isolate the causative organism in osteomyelitis, with concordance rates reported of 26% to 44%, a false-negative rate of 52%, and a false-positive rate of 36%.[1,16,81–84] When obtaining open biopsy specimens intraoperatively, it is necessary for the surgeon to send soft tissue and bone specimens for microbiologic evaluation, because only 36% of soft tissue cultures accurately identify the bone pathogen.[20] Intraoperative frozen sections can be useful. Greater than 5 to 10 neutrophils per high power field is highly suggestive of acute deep infection.[4] Blood cultures can identify the causative organism in up to 50% of cases of hematogenous osteomyelitis.[16]

Percutaneous bone biopsy may be considered to obtain bacteriologic culture and sensitivity data when prolonged medical treatment is indicated. To accurately interpret these data, antibiotic therapy must be discontinued for 2 to 4 weeks prior (to avoid a false-negative result) and the needle must be inserted through normal skin, avoiding all ulcers or areas of soft tissue infection, to obtain the bone sample.[10] Percutaneous biopsy under CT guidance may be helpful in accurate anatomic localization over fluoroscopic guidance. The current recommendation of the Infectious Diseases Society of America is that percutaneous bone biopsy only be considered in the following circumstances: (1) uncertainty regarding the diagnosis of osteomyelitis despite clinical and imaging evaluations, (2) absent or unclear culture data from soft tissue specimens, (3) failure of empiric antibiotic therapy, and (4) a desire to use antibiotic agents that may be especially effective for osteomyelitis but have a high potential for selecting resistant organisms.[54]

TREATMENT OF OSTEOMYELITIS

Effective management of osteomyelitis is best achieved with a multifaceted approach involving medical optimization of the patient's physiologic status; infectious disease consultation for targeted antibiotic therapies and treatment durations; and surgical specialists for debridement, revascularization, wound care, and soft tissue or limb reconstruction when necessary. Antibiotic suppression is most effective when broad-spectrum empiric antibiotics are initiated early and therapies are then tailored with the help of an infectious disease specialist as culture and sensitivity data become available.[6,19,33,85] Collaboration with a primary care provider to optimize the patient's physiology and comorbid conditions is essential for successful management of

Table 3
Summary of imaging modalities, characteristic findings, and clinical application in osteomyelitis

Imaging Modality	Findings of Osteomyleitis	Clinical Application
Plain radiographs	Periosteal reaction, sequestra, cortical destruction, loss of trabecular organization, soft tissue swelling	Appropriate initial imaging study Provides information on foot alignment, joint congruency, and bony architecture Repeat radiographs in 2–4 wk when clinical suspicion persists
CT	Periosteal reaction, sequestra, cortical destruction, soft tissue swelling, sinus tracts, intramedullary gas foci, foreign bodies	Provides excellent anatomic definition of cortical bone Study of choice to localize infection when MRI is unavailable
Tc-99m MDP bone scan	Increasing uptake in affected area over all three phases: blood-flow phase, blood-pool phase, and bone phase (in cellulitis, high uptake only seen during blood-flow and blood-pool phases)	Findings evident within 24–48 h of symptom onset Limited specificity because of uptake of radiotracer at all sites of increased bone metabolism May add fourth phase at 24 h in patients with early, mild intensity uptake to increase accuracy
Gallium-67 citrate scan	Increased accumulation of isotope in affected areas (gallium binds to acute-phase reactants, taken up by leukocytes and used by bacteria for iron metabolism)	Normal gallinium scan virtually excludes osteomyelitis, therefore useful postdebridement to confirm eradication False-positives may occur in areas of bone healing, neoplasms, neuro-osteoarthropathy, and around prostheses

Indium-111–labeled leukocyte scan	Neutrophils accumulate at areas of acute infection by chemotaxis and diapedesis	Useful when coexisting fractures, cellulitis, or osteoarthopathy is present Chronic infections not well imaged, because monocytes and lymphocytes predominate Indium-111 leukocyte scan combined with Tc99m bone scan is the modality of choice in posttraumatic and nonunion site osteomyelitis
FDG-PET	Increased accumulation in areas with increased intracellular glucose metabolism	Highest accuracy imaging study in chronic osteomyelitis Poor spatial resolution, therefore combined with CT scan (PET/CT) for excellent anatomic detail PET/CT is imaging study of choice when MRI is equivocal or hardware scatter complicates imaging
MRI	In acute osteomyelitis T1: low signal intensity in bone marrow, determine osseous extent T2/short-tau inversion recovery: high signal intensity in bone marrow, sinus tracts, and soft tissue inflammation In chronic osteomyelitis "Rim sign," well-defined rim of high signal intensity surrounding active disease focus	Imaging study of choice in osteomyelitis Gadolinium contrast improves anatomic detail of soft tissues

osteomyelitis. These include tight glycemic control, tobacco cessation, treatment of hepatic and/or renal dysfunction, and optimization of the patient's nutritional status.[1,5,23,31,86–89] When indicated, aggressive arterial reconstruction of the limb results in improved wound healing and a five-fold increase in limb salvage.[11] The foot and ankle surgeon must consider optimization of foot biomechanics, including tendoachilles lengthening, correction to a plantigrade foot, appropriate footwear or orthoses, and preservation of the soft tissue envelope with avoidance of bony pressure or contact points.[90]

Surgical Management

Key principles of surgical treatment of osteomyelitis involve complete debridement of all devitalized tissue, stabilization of the bone and soft tissues, appropriate specimen collection and antibiotic delivery, and a well-vascularized soft tissue envelope covering contact points. Surgical debridement is indicated in the presence of an abscess, necrotic tissue, systemic indicators of sepsis, or failure to improve despite adequate antibiotic therapies.[1,31] Numerous factors including site and extent of infection, physiologic status of the patient, and surgeon preference formulate the surgical treatment. Surgical debridement and antibiotic therapy historically achieved success rates nearing 70%.[91–93] Advances over the past 40 years including the use of antibiotic cement, advances in soft tissue procedures, improved bone grafting techniques, and multiplanar external fixator techniques have led to success rates greater than 90%.[94–102]

Surgical debridement removes all nonviable tissue in an expansive manner with a focus on preserving blood supply to the area. Bony debridement should remove necrotic, sclerotic, and avascular bone while minimizing periosteal stripping. Bone resection proceeds until pinpoint bleeding bone (Paprika sign) is encountered.[17] Wide debridements, with serial debridements when necessary, are preferable to leaving nonviable tissue behind despite the size of defect created.[17,31]

Bony stability must be assessed and restored. External fixation is frequently used to provide stabilization while keeping the infected area free of surface implants that may become colonized. A newer technique that has shown effectiveness in small studies is the use of antibiotic coated intramedullary nails.[99,100,103] Although this technique provides for some stabilization of the bone, it is typically supplemented with additional procedures or methods to address the tissue and bony dead space.

There are multiple options for the management of bony defects. Antibiotic cement beads are often used to provide high local antibiotic concentrations (up to 200 times higher than systemic antibiotic levels) with lower systemic toxicity and fill dead space.[31,104] Antibiotic beads made of polymethylmethacrylate and clindamycin, vancomycin, and/or tobramycin have been shown to have the highest local bioavailability and elution.[97] Bacteriocidal levels of antibiotics are maintained for 2 to 4 weeks, at which time the beads can be removed and replaced with cancellous bone graft or vascularized bone graft. This technique and its many variations have success rates near 90%.[101,102,105,106] Autograft cancellous grafts can be harvested from the calcaneus, proximal tibia, and iliac crest. Novel techniques allow harvest of autograft cancellous bone graft from the intramedullary canal using the Reamer/Irrigator/Aspirator device (DePuy Synthes, Paoli, PA). Allograft cancellous graft is widely commercially available. Structural (corticocancellous) grafts can be obtained with or without a vascular pedicle from the iliac crest, fibula, ribs, and scapula. The utility and efficacy of osteoinductive and osteoconductive materials, such as bone morphogenic proteins, demineralized bone matrix, and various calcium scaffold complexes for management of bone defects in the setting of osteomyelitis, are currently being explored.

In certain situations of extensive bone loss, the Ilizarov technique of external fixation with distraction osteogenesis has the benefit of stabilizing the bone and providing a mechanism for managing the bony defect.[107–109] In this technique, the bony defect is eliminated by bone transport or acute shortening of the limb followed by distraction osteogenesis at a distant corticotomy site to regain the lost length. This technique can also be combined with intentional deformity, which is frequently used to allow for closure of the soft tissues overlying the site of the defect without the need for muscle flap or free flap coverage.[110] In this technique, the deformity is then slowly corrected allowing for tissue stretching after healing of the wound.

An essential component of the treatment of osteomyelitis is closure or coverage of any soft tissue defects to allow for adequate blood flow to the area. Consultation with a reconstructive plastic surgeon or an orthopedic surgeon familiar with management of soft tissue defects may be necessary. Multiple options exist for coverage of defects including rotational muscle flaps, free muscle, and fasciocutaneous flaps.[111–113]

Indications for amputation include arterial insufficiency, major nerve paralysis or paresthesias, and severe joint contractures or stiffness that renders the limb nonfunctional.[31,90,114] Patient factors associated with amputation include previous ulceration (OR, 0.23), HgA_{1c} greater than 7.4 (OR, 5.9), soft tissue infection accompanying osteomyelitis (OR, 5.9), peripheral arterial disease (OR, 6.2), and skin necrosis (OR, 12.2).[45]

Adjunctive Therapies

Several adjunctive therapies may be considered. Hyperbaric oxygen therapy affects the microenvironment of wounds and has been shown to promote healing in diabetic wounds through its antiedema, antibacterial, and neovascularization effects.[115,116] In hyperbaric conditions, wound tissue oxygen tension can be increased 10- to 15-fold, which stimulates fibroblast proliferation, collagen production, neovascularization, and epithelialization, and has direct lethal effects on anaerobic organisms.[1,116,117] Hyperbaric oxygen therapy may prove useful as an adjunctive therapy in the treatment of osteomyelitis.[31,116,118] Growth factors, such as bone morphogenic proteins, enhance bone healing and callous formation at infection sites.[119] Platelet-rich plasma and leukocyte- and platelet-rich plasma gel have demonstrated faster healing times, eradication of infection, positive synergy with antibiotic therapy, and antimicrobial effects in several animal models and case studies.[120–123] Some studies using pulsed electromagnetic fields and ultrasound suggest these physical energy modalities may directly interfere with biofilm formation, increase bone formation and maturation, accelerate soft tissue healing, and work synergistically with antibiotic therapies to increase their efficacy.[124–128] Further research is needed on the efficacy and application of these adjunctive therapies for clinical use in osteomyelitis of the foot and ankle.

SUMMARY

Osteomyelitis of the foot and ankle is a common, potentially devastating condition with diagnostic and treatment challenges. An understanding of the epidemiology and pathogenesis of osteomyelitis can raise clinical suspicion and guide further testing and treatments. History and physical examination, laboratory studies, vascular studies, histologic and microbiologic analyses, and various imaging modalities contribute to the diagnosis and treatment. Treatment should take a multidisciplinary approach to optimize patient factors, ensure eradication of the infection, and restore function. Empiric broad-spectrum antibiotic treatment should be included in early, aggressive treatment, with later antibiotic regimens tailored according to culture and sensitivity

data. Surgical treatment needs to consider physiologic factors of the infection and patient, must be extensive, and may use multiple techniques to achieve successful outcomes. Optimization of vascular status, soft tissues, limb biomechanics, and the physiologic state of the patient must all be considered to accelerate and ensure healing. Adjuvant therapies and novel laboratory markers may enhance outcomes as they are further studied and applied clinically.

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