Osteomyelitis of the Foot and Ankle in the Diabetic Population: Diagnosis and Treatment

Authors: Brandon E. Crim, DPM [1], Dane K. Wukich, MD [2]

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Abstract: Diabetes is a disease with many manifestations secondary to hyperglycemia which include peripheral arterial disease, peripheral neuropathy, and immune dysfunction. Osteomyelitis is often found in diabetic patients, and can be difficult to treat in this complex and growing patient population. The following article serves to survey the literature as to the diagnosis and treatment options for diabetic patients with osteomyelitis, as well as stress the importance of further studies to clearly define and properly treat osteomyelitis in the diabetic population.

Key words: Diabetes, osteomyelitis, foot infection, ulceration, peripheral neuropathy.

Address correspondence to : Dane K. Wukich, MD
Assistant Professor of Orthopaedic Surgery. Chief, Division of Foot and Ankle Surgery. University of Pittsburgh Medical Center, Department of Orthopaedic Surgery. Director, UPMC Comprehensive Foot and Ankle Center. Pittsburgh, PA.
wukichdk@upmc.edu

[1] Resident. University of Pittsburgh Medical Center. Pittsburgh, PA
crimbe@upmc.edu
[2] Assistant Professor of Orthopaedic Surgery. Chief, Division of Foot and Ankle Surgery. University of Pittsburgh Medical Center, Department of Orthopaedic Surgery. Director, UPMC Comprehensive Foot and Ankle Center

Introduction

The growing diabetic population is one of the most important issues facing health care providers today. The prevalence of diabetes has increased by 61% between 1990 and 2001, and it is estimated this number will further increase by 165% between 2001 and 2050.[1] Diabetes is a disease with many manifestations secondary to hyperglycemia due to lack of insulin production, insulin resistance or both. Peripheral arterial disease (PAD), neuropathy, nephropathy and immunopathy are among the major comorbidities of the disease. It is estimated that 15 % of diabetic patients will develop a plantar ulcer in their lifetime due to neuropathy.[2] Soft tissue and bone infection often accompanies ulceration, and is a leading cause of both hospital admissions as well as lower extremity amputations.[2]

Osteomyelitis is a significant concern in diabetic patients with open wounds. Unfortunately, there are no clear guidelines as to the definition or the diagnosis of osteomyelitis.[3] The following article serves to survey the literature as to the diagnosis and treatment options for diabetic patients with osteomyelitis, as well as stress the importance of further studies to clearly define and properly treat osteomyelitis in the diabetic population.

Risk Factors for Osteomyelitis

Several risk factors predispose diabetic patients to developing bone infection. Compared with nondiabetic cohorts, diabetic patients are at an 80% increased risk of cellulitis, a four-fold increased risk of osteomyelitis, and a two-fold risk of both sepsis and death caused by infection.[4] Peripheral neuropathy is a significant independent risk factor for diabetic foot ulceration.[5] A large center recently reported that 12 % of ulcer patients had osteomyelitis while 20% of diabetic foot infections were associated with osteomyelitis.[6] In the United States, 10% of diabetic patients may show signs of neuropathy at the time of diagnosis of diabetes, and 40 % will shows signs of neuropathy within the first decade of diagnosis.[7] Loss of protective sensation places a patient at a seven -fold increase risk of ulceration and unrecognized trauma. Osteomyelitis almost always occurs through direct inoculation from existing foot ulcerations. Microorganisms that colonize wounds or that are found in adjacent soft tissue infections violate the periosteal borders of bone, and devitalize the cortex resulting in bone infection.

Peripheral artery disease is also a significant independent risk factor for diabetic foot ulcers.[5] It has been well documented that patients with diabetes are at a higher risk for both large and small vessel angiopathy.[7] Vasculopathy leads to poor tissue perfusion, local hypoxia and a poor environment for both soft tissue and bone healing. It is imperative during the physical exam that an attempt is made to palpate both the dorsalis pedis and posterior tibial pulses. The inability to palpate these pulses should lead clinicians to order non-invasive vascular studies.[8] An ankle brachial index (ABI) of <0.90 is suggestive of vascular compromise. Diabetic patients are more prone to Mockeberg's medial calcific sclerosis which can falsely elevate the ABI studies. An ABI >1.1 is due to noncompressible vessels, and suggestive of calcific sclerosis.[8] Absolute toe pressures may be useful in patients with falsely elevated ABI since digital vessels are less likely to undergo medial calcinosis.

Transcutaneous oxygen pressures ($TcPO_{2)}$ are helpful in determining the prognosis of wound healing. A $TcPO_2$ of < 30 mmHg indicates poor potential for wound healing.[8] Doppler wave forms and segmental leg pressures may assist in the identification of vascular lesions. It is imperative that patients diagnosed with osteomyelitis have adequate blood flow in order to treat the bone infection, and patients with abnormal physical findings and/or non-invasive tests should undergo consultation with a vascular surgeon.

Another independent risk factor for osteomyelitis is structural deformity of the foot.[5] Boney prominences, with or without neuropathy, can cause ulcerations that lead to direct inoculation of bone. Examples of structural deformities include hammertoes, digital contractures, ankle equinus, pes cavus and osseous prominence from Charcot neuroarthropathy. Bevan et al. were able to identify a radiographic risk factor for hyperkeratosis and ulceration in patients with Charcot neuroarthropathy.[9] They reported that lateral weight bearing radiographs of the talo-1st metatarsal angle (Meary's angle) greater than -27 degrees was associated with midfoot breakdown. It is imperative that structural deformities should be addressed in patients who are at high risk for ulceration or in patients who experience recurrent ulceration. Traumatic risk factors for osteomyelitis include puncture wounds, lacerations, open fractures and improperly fitting shoe wear.

Clinical Diagnosis

The diagnosis of osteomyelitis in diabetic patients can be difficult due to unreliable clinical signs and laboratory values. The diagnosis may be more obvious in patients who present with an ulcer that has extruded pieces of bone. Patients may not present with any signs or symptoms until the infection is life or limb threatening.

Signs of inflammation may be absent in up to two thirds of ulcers with histopathological evidence of osteomyelitis.[4] Immunopathy due to impairment of leukocyte phagocytosis and chemotaxis may be present in diabetic patients, and is often overlooked in this patient population.[2] Signs of inflammation or infection include erythema, warmth, purulence, drainage from wound, malodor, lymphangitis and gangrene.[2] Osteomyelitis should always be considered when ulcerations fail to heal properly.[10] Forty-five percent of diabetic ulcers occur in the toes, 45% in the metatarsals, 4.5% calcaneus and 1.5% in the midfoot. Consequently, osteomyelitis of the forefoot is the most likely anatomically involved region.[11] Midfoot and rearfoot osteomyelitis is less common, and can be more difficult to treat.

One clinical test which has been relied on over the past 14 years is the probe to bone test. In 1995, Grayson described using a sterile blunt metal probe to determine if bone could be felt through an ulceration site.[12] The results of the study showed a sensitivity of 66%, and a specificity of 85% in diagnosing osteomyelitis. They reported an 89% positive predictive value and a 56% negative predictive value. The conclusion drawn from the study was if the ulcer probed to bone, more than likely it represented osteomyelitis and advanced imaging studies were unnecessary. More recently, Shone et al. reported a positive predictive value of only 53% and a negative predictive value of 85%.[13] The dramatic difference between the positive predictive values in the two studies can be accounted for when the patient population is analyzed. In the Grayson study, 66% of patients were considered to have osteomyelitis and largely consisted of hospitalized patients. Bone biopsy was not performed on all patients, and the diagnosis was based on radiological findings, surgical exploration, and histological findings of inflammatory cells, fibrosis, bone necrosis and reactive bone as opposed to microbiological studies. In the Shone study, only 20% of the patient population was diagnosed with osteomyelitis.

In another recent large study by Lavery et al. reporting on 1666 diabetic patients, the probe to bone test had a positive predictive value of 57% and a negative predictive value of 98%.[6] The conclusion drawn from this study was that a positive probe to bone test only slightly increases the probability of osteomyelitis versus a coin flip. A negative probe to bone test however, is a strong predictor for the absence of bone infection. These studies clearly outline the importance of the patient population in any study, and stress the importance of prevalence in assessing the validity of any test.

The gold standard for diagnosis of osteomyelitis has been through bone biopsy. The sensitivity and specificity have been reported at 95% and 99% respectively.[6,14] Sampling error may occur when biopsy is performed, since false negatives do occur. On histopathological analysis, one can see signs of osteonecrosis. On micropathological analysis, one can identify both acute and chronic processes. Acute infection will show infiltration of neutrophils, while chronic infection will show plasma cells and lymphocytes. When bone cultures are being obtained, it is recommended that antibiotics be withheld for at least 48 hours prior to culturing. Soft tissue pathogens may not always reflect the organisms involved in underlying osteomyelitis, mandating that both deep soft tissue and bone be sent for analysis. Ge et. al. found that 75% of wounds had multiple organisms, with an average of 2.4 organisms per wound.[15] Lavery and Sariaya found that only 36% of soft tissue cultures correctly identified bone pathogens, even with sampling during the same surgical procedure. They found an average of 2.25 pathogens per bone biopsy, with more than one organism in 83% of patients.[14]

In 1991, Newman et al. reported that osteomyelitis was likely if diabetic ulcers were greater was than 2 cm^2, deeper than 3mm or had exposed bone.[16] Certain laboratory markers may assist in the diagnosis of osteomyelitis. An increase in the white blood cell count of patients may assist in the diagnosis of infection, however, Armstrong et al. stated that leukocytosis was infrequent in patients with diabetes with acute osteomyelitis.[17]

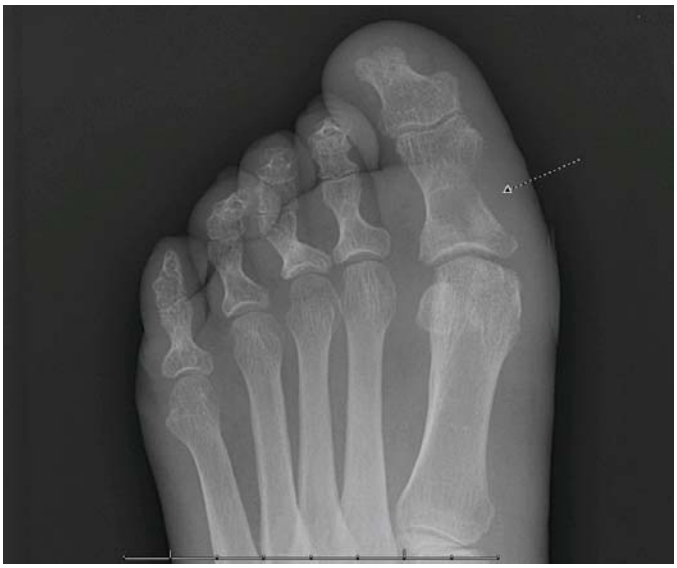

Figure 1 Radiograph of 52 year old patient with history of diabetes and ulceration of the left forefoot. Note the medial cortical destruction of the proximal phalanx of the hallux with the presence of radiolucency which can be found in osteomyelitis.

Butalia et al. concluded that an erythrocyte sedimentation rate > 70 mm/hr significantly increases the probability of osteomyelitis.[18] Often the diagnosis of osteomyelitis in the face of acute soft tissue infection can be difficult to differentiate from Charcot neuroarthropathy. In patients with neuropathy, including those with diabetes, C-reactive protein (CRP) can be a useful laboratory parameter. C-reactive protein level is often elevated with osteomyelitis and infection, but is not elevated in patients with Charcot foot.[10] Fleischer et al. determined that a combination of clinical and laboratory markers can be a sensitive strategy for clinicians to detect early osteomyelitis in the diabetic population.[19] They compared over 30 clinical and laboratory tests to determine which was most helpful in the diagnosis of acute osteomyelitis in a population of 54 diabetic patients presenting with infected ulcerations. They concluded that an ulcer depth greater than 3 mm and a C-reactive protein greater than 3.2 mg/dL were the most helpful in differentiating osteomyelitis from cellulitis.

While an elevated ESR was a helpful marker for infection, CRP was the most sensitive single test for acute osteomyelitis. New markers are being used in order to diagnose and monitor infection. Procalcitonin is a marker which has been shown to increase in patients with infection, however, further studies are warranted to assess its validity in patients with osteomyelitis.[10]

Imaging

Imaging studies must be interpreted in concert with the clinical exam and laboratory values to assist in the diagnosis of osteomyelitis. Plain film radiography should be the first imaging modality of choice. Although the sensitivity and specificity are lacking, they are easy to obtain and relatively inexpensive in comparison to other imaging choices. Osteomyelitis appears as permeative radiolucencies, destructive changes, cortical defects and / or periosteal new bone formation.[20] (Fig. 1)

The specificity of plain film radiography tends to be higher than its sensitivity, but can be compromised by nonspecific osseous reactions.[21] The appearance of these findings can often be difficult to differentiate from other pathological processes such as Charcot neuroarthropathy, gout, and many connective tissue diseases. Unfortunately, plain film radiographic signs of osteomyelitis may be lacking in the first few weeks, as it takes 30-50% bone loss before evident on radiographs. Plain film radiography is a useful modality to rule out foreign bodies and gas in the soft tissues, known as emphysema.

Bone scans with Technetium- 99 methylene diphosphonate [Tc^{99m}] detect changes in bone in a more timely fashion when compared to plain film radiographs. The sensitivity for this imaging modality using three- or four-phase scans approaches 90% which is an improvement over plain film radiography.[4]

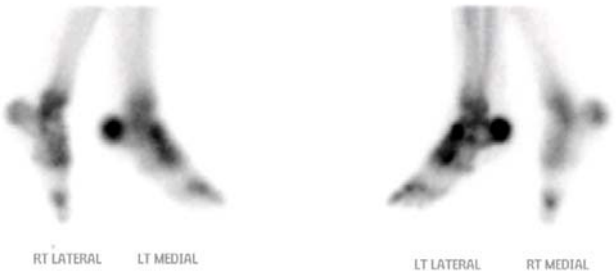

Figure 2 Bone scan which shows focal area of increased uptake centered around hallux of left foot.

The specificity is much lower averaging less than 50% and is secondary to increased bone turnover in most bone disorders such as fractures, Charcot arthropathy and postoperative changes. The specificity improves with white blood cell labeled studies because they accumulate in areas of infection as opposed to areas of increased blood turnover.[4] (Fig. 2) White blood cell studies also can monitor response to therapy as radionuclide uptake decreases with resolving infection.[4,22] These studies however are expensive and time consuming, and can be limiting due to poor anatomic resolution. Distinguishing between osteomyelitis and Charcot neuroarthropathy can be difficult due to increased uptake of labeled WBC due to marrow reactivation. Improved specificity may occur with sulfur colloid scanning.[22]

Magnetic Resonance Imaging (MRI) can aide in the diagnosis of diabetic osteomyelitis due to altered signal intensity of affected bone. MRI is helpful in patients with surrounding soft tissue infection because it captures both soft tissue and bone. Sensitivity of MRI is reported between 90-100%, while specificity ranges between 80-100%.[4] The normal high signal intensity of T1 image due to marrow fat in bone is replaced with decreased signal intensity (see Fig. 3), while the T2 image which is typically darker in healthy bone shows increased signal intensity (see Fig. 4).

Several other pathological processes such as fracture, Charcot neuroarthropathy, arthritis, and neoplasms can show similar changes on MRI. It is important to correlate MRI results with the clinical picture as well as laboratory values. Although costly, MRI has great anatomical detail and is a useful tool in operative planning.

Kapoor et al. recently conducted a meta-analysis on the usefulness of MRI in diagnosing foot osteomyelitis.[21] Sixteen studies met their inclusion criteria in order to compare the performance of MRI versus bone scan, white blood cell scanning, and plain film radiography. Eleven of the 16 studies were comprised almost exclusively of diabetic patients. MRI was shown to have a sensitivity of 90% and a specificity of 83%, with an overall accuracy (the weighted average of the sensitivity and specificity) of 89%. MRI was found to be superior to plain radiography, Tc bone scanning and labeled white cell scans in diagnosis foot osteomyelitis.

In a meta-analysis by Dinh et. al., MRI was found to be the most accurate imaging test for diagnosis of osteomyelitis.[20] The diagnostic odds ratio was found to be 24.36, compared to 2.84 for plain film radiography, 2.10 for bone scanning, and 10.07 for leukocyte scanning. These results demonstrate excellent diagnostic power with MRI as compared to other imaging modalities.

According to Dinh, both CT and positron-emission tomography (PET) have not been adequately tested in the diabetic population to recommend their use for diagnosis of osteomyelitis.[20] Studies in this patient population have lacked either histopathological examination or cultures to diagnose osteomyelitis. PET scanning is a newer technology that shows promise for treating bone infection in the future.

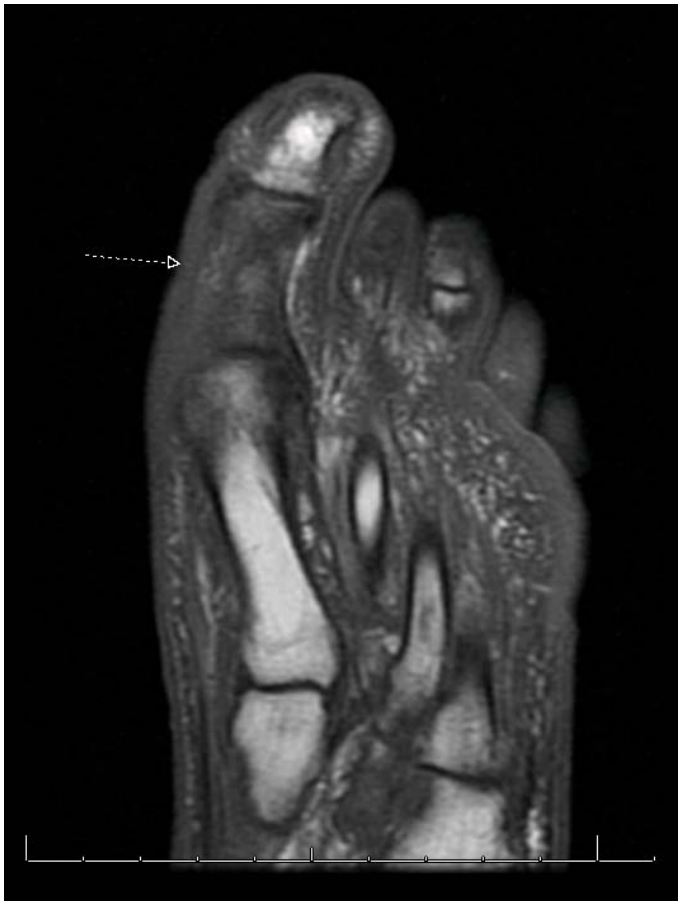

Figure 3 T1 image which demonstrates loss of signal intensity which is consistent with osteomyelitis of the proximal phalanx of the hallux with involvement of the distal first metatarsal head.

Non-Surgical Management

The underlying principle behind non-surgical treatment is to administer antibiotics while providing a local environment in which the medication can work.[23] Antibiotic therapy should be as targeted and as narrow spectrum as feasible, with the assistance of bone cultures when possible.[24] Senneville et al. found that bone culture based antibiotic therapy was the only variable associated with remission (greater than 12 months) using both univariate and multivariate analysis in 50 patients.[25] Unfortunately, no antibiotic has been shown to be superior in the eradication of osteomyelitis.[23,24]

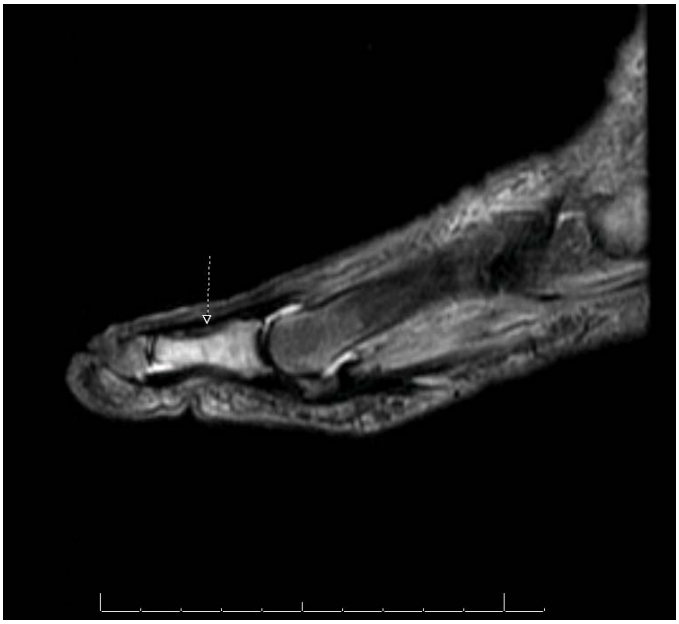

Figure 4 T2 image which clearly shows marrow edema of proximal phalanx of hallux in patient with osteomyelitis.

It is imperative to cover staphylococcus due to its high prevalence, with coverage of methicillin resistant staphylococcus following its culture or due to local prevalence data. Game and Jeffcoate found that MRSA colonization was linked with prior hospitalization.[3] No particular route, either parenteral or oral, has been shown to be either superior or inferior to the other.[23,24] Adequate levels of antibiotics can be achieved through intravenous (IV) or highly bioavailable oral medications. Although the length of antibiotic therapy is frequently discussed in the literature, there is no hard data to guide decision making as to the duration of treatment. Classically, four to six weeks of parenteral antibiotics is utilized in conjunction with debridement to eradicate osteomyelitis. More recently, reports have shown it is possible to have a shorter treatment with parenteral and longer treatment with oral therapy. Currently, there is no substantial scientific evidence that lays forth a protocol of medical therapy that gives a consistent, predictable result.[2]

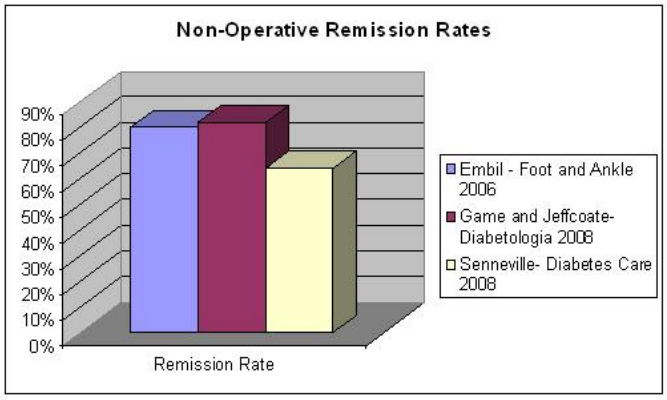

Figure 5 Non-operative remission rates reported in recent literature.

Game and Jeffcoate reported on 113 patients who were treated non-surgically with antibiotic therapy.[3] Oral therapy was chosen for 80% of patients, while the other 20% received IV followed by oral antibiotics. The mean duration of therapy for oral treatment was 9 weeks, while the IV group had a mean duration of 2 weeks. Overall, 93 of 113 (82%) were in remission at 12 months. The results of this study concur with the results reported in a study by Embil et al. who treated diabetic osteomyelitis with oral therapy in 79 patients.[11] Patients were treated with a mean of 3 oral antibiotics, and duration lasted an average of 40 weeks. With this therapy, 80 % patients achieved remission with a mean relapse free period of 50 weeks. Data from these current studies suggest that primarily non-surgical management can be successful in the treatment of diabetic osteomyelitis.[3,11] (Fig. 5)

Surgical Management

In order to understand surgical management of osteomyelitis, several terms must be clearly defined. The problem with many reported studies dealing with osteomyelitis is the unclear definition of surgical treatment. Debridement is defined as the removal of non-viable infected or necrotic soft tissue surrounding a wound with underlying osteomyelitis.

Conservative surgery is defined as the removal of infected bone with or without the resection of surrounding soft tissue, while amputation is the removal of a portion of the lower extremity. Amputation can be subdivided into two categories: minor amputations and major amputations. Minor amputations consists of the removal of a portion of the foot distal to the ankle joint, while amputations proximal to the ankle joint are known as major amputations. Depending on the degree of soft tissue and underlying bone involvement, the surgeon must decide whether debridement or amputation is warranted.

Whether or not one treats diabetic patients with osteomyelitis non-surgically or surgically, all infected ulcerations should be debrided with the drainage of any obvious purulence. Debridement of the wound aides in the healing process by converting a chronic wound to an acute wound as well as allowing the clinician to properly visualize the wound bed. Debridement also allows for the removal of devitalized tissue that helps rid the area of a nidus for infection. Simple incision and drainage can occur at bedside, in the clinical setting, or in the operating room. While many diabetic patients are insensate, some may require anesthesia for adequate debridement. There are several indications for surgical management of diabetic foot osteomyelitis. Patients who have failed non-surgical treatment with either oral or intravenous antibiotics should undergo surgical treatment. Patients with abscess formation, necrotizing fasciitis or gangrene should also be surgically treated.

The foot and ankle surgeon must keep in mind several key concepts when treating diabetic patients with osteomyelitis. Medical clearance should be obtained unless an emergent situation such as gas gangrene or necrotizing fasciitis exist. The surgeon should debride to bleeding viable bone, resecting all infected and necrotic bone.

Wide excision of bone with margins >5 mm have been shown to reduce the recurrence rate in chronic osteomyelitis as opposed to marginal or limited resection <5 mm.[26]

Partial or minor amputation is preferred over transtibial amputation for several reasons. Gait is more normal after minor amputations, and less energy is required to ambulate.[27] Patients with distal amputations also appear to have improved quality of life.[28] Finally, increased morbidity and mortality is associated with more proximal major amputations.[29,30]

Grossly infected wounds should be left open or treated with negative pressure wound therapy, and repeat debridements are often necessary.[31-33] If the infected bone is resected along with all soft tissue involvement, primary closure is an option. Antibiotic impregnated beads are beneficial in the face of infection, and can aid in filling a dead space left by resection of tissue. If delayed primary closure is impossible, negative pressure therapy or skin grafts and flaps may be beneficial for closure.[31] Following surgical debridement, culture guided antibiotic coverage should begin for duration of 2-6 weeks.

Ha Van and colleagues in a 1996 cohort study reported on the contribution of conservative surgery versus non-surgical management of diabetic foot osteomyelitis.[34] One group was treated non-surgically with offloading, antibiotic therapy, and wound care. The other cohort was treated similarly with the addition of surgery, which was defined as the resection of a phalanx or metatarsal bone. The non-surgical group had a healing rate of 57%, with a mean time of 462 days. The conservative surgical group showed a healing rate of 78% with an average of 181 days to wound closure. The number of secondary surgical procedures, which included amputation and revascularization, was significantly higher in the non-surgical cohort. Also, the duration of antibiotic usage was much higher in the nonsurgical group - 246 days versus 111 days with the surgical cohort.

Conclusion

In order for any disease or pathology to be treated, it must be clearly defined. What is diabetic foot osteomyelitis? Is it soft tissue infection with changes found on plain film radiography, or should more advanced imaging studies be required? In order to diagnose osteomyelitis, does one need the “gold standard” bone biopsy, and should there be histopathological change?

When surveying the literature, it is clear there is no true consensus on the diagnosis of osteomyelitis, both in the diabetic as well as the non-diabetic population. We face a population of patients with many comorbidities and risk factors who are at a substantial risk for lower extremity infection. It is imperative that osteomyelitis be clearly defined and understood by all clinicians in the care of diabetic patients, as well as the population as a whole.

Currently, there is no conclusive evidence to suggest whether medical therapy alone is sufficient to treat osteomyelitis and when surgical management is indicated.[10,35] Surgical debridement of infected bone appears to be unnecessary in some cases of diabetic foot osteomyelitis; however, at the present time we cannot predict which cases of osteomyelitis will respond to medical therapy with certainty.[23]

Randomized controlled trials are needed in order to compare surgically and non-surgically treated diabetic patients with osteomyelitis. It is through these studies that we can determine the proper treatment regimen to treat this difficult challenge in a growing patient population.

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