

An evidence-based approach to diabetic foot infections

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Abstract

Foot infections are a major complication of diabetes mellitus and contribute to the development of gangrene and lower extremity amputation. Recent evidence indicates that persons with diabetes are at greater risk for infection because of underlying neuropathy, peripheral vascular disease, and impaired responses to infecting organisms. This article reviews the underlying pathophysiology, causes, microbiology, and current management concepts for this potentially limb-threatening complication. Multidisciplinary management consisting of teams of specialists with a focus on limb preservation can make significant improvements in outcomes, including a reduction in rates of lower extremity amputation. © 2003 Excerpta Medica, Inc. All rights reserved.

*The germ is nothing. It is the terrain in which it is found
that is everything.*

—Louis Pasteur, 1860

Foot infections are a frequent complication of persons with diabetes mellitus, accounting for up to 20% of diabetes-related hospital admissions [1]. Foot ulcers are even more common, developing in approximately 15% of all persons with diabetes during their lifetimes [2,3]. Although infection is rarely a component cause in the pathway leading to ulceration, it is certainly a significant underlying risk factor for lower extremity amputation (LEA) [4,5]. Infection frequently develops in existing diabetic foot ulcers and can have an adverse effect on their outcomes [6,7]. One prospective cohort study found that approximately 15% of patients with diabetes who developed foot ulcers also developed underlying osteomyelitis [8]. A total of 16% of ulcerated patients went on to LEA at some level, presumably because of unresolved infection or tissue loss.

Nontraumatic LEA is an increasingly frequent complication in this high-risk population despite recent efforts to reduce its frequency. Foot ulcers precede approximately 85% of all nontraumatic lower limb amputations in persons with diabetes [2]. In 1996 there were 86,000 hospital discharges (excluding Veterans Administration and military hospitals) in the United States for diabetes-related LEA [9,10]. Recognizing that this figure actually is an underestimation of the true numbers of amputations performed, it is disturbing to see that these numbers have been increasing

since such national data were first collected in 1980. Although not specifically recorded, an optimistic viewpoint might be that the increased frequency of such amputations might reflect an emphasis on limb salvage by the performance of greater numbers of minor or partial foot amputations. Estimating a low average cost (direct and indirect) of a diabetes-related amputation at \$24,000, these 86,000 LEAs represent a cost of >\$2 billion annually for this single complication of diabetes [3,10,11].

Several studies have elucidated the significance of infection as a predisposing risk factor leading to amputation, often in concert with peripheral neuropathy, peripheral vascular disease, and foot ulceration [5,12-14]. In a study of veterans with diabetes undergoing LEA, infection was a frequent component cause in the pathway to amputation, with 59% of the cases attributed to this factor [5]. In a case-control study from the same group, infection was a significant predisposing risk factor for amputation in 68% of the cases [15]. In a Swedish study of 223 diabetic patients with severe foot infections, approximately 50% required amputation at some level before healing or death [12]. Only 10% of these, however, were major amputations because of a multidisciplinary focus on limb preservation. In another prospective study of LEA in veterans with diabetes, there were significantly more infections, or history of lower extremity infections, in those patients undergoing amputation compared with those who did not have this outcome [13].

Despite a long-held belief that persons with diabetes have more infections than nondiabetic persons, strong clinical evidence has been lacking in this regard [16,17]. However, a very recent population-based retrospective cohort

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study from Toronto has shed new light on this question [18]. Two cohorts of almost 514,000 each were studied, one with diabetes and one without. Nearly 50% of all persons with diabetes had a hospitalization or physician claim for an infectious disease compared with 38% in the matched nondiabetic group. The risk ratio was 1.21 (99% confidence interval [CI], 1.20–1.22; $P < 0.0001$) even when repeated for 2 separate years. Although the majority of patients were treated as outpatients, 5.2% of the diabetic cohort compared with 2.6% of the nondiabetic cohort required hospitalization. Therefore, the risk ratio for infections requiring hospitalization was 2.01 (99% CI, 1.96–2.06; $P < 0.0001$). The diabetic cohort also had an 80% increased risk for cellulitis, a >4-fold increased risk of osteomyelitis, and a 2-fold increased risk for sepsis. In addition, death attributable to any infectious disease was more prevalent in diabetes, with a risk ratio of 1.84 (99% CI, 1.73–1.95, $P < 0.0001$). Clearly, the results of these data suggest that infection is indeed a significant complication of diabetes [18].

Pathophysiology

Although not all foot infections are the result of bacterial invasion of ulcerations, this sequence of events is a common pathway leading to serious diabetic lower extremity sepsis. Predisposing factors for limb-threatening lower extremity infection are similar to those for ulceration and include neuropathy, macrovascular and microvascular impairments, as well as decreased resistance to infection, which is often referred to as immunopathy [19–21].

Loss of protective sensation resulting from peripheral sensory neuropathy is a very prevalent complication of diabetes and is a leading risk factor for both ulceration and amputation [6,7,20,22,23]. Motor and autonomic fibers are also typically involved with “glove and stocking” distal symmetrical neuropathy. The former will result in intrinsic muscle atrophy or drop foot as well as structural deformities, such as clawtoes. High plantar foot pressures frequently ensue, which have also been linked to foot ulceration [24]. Autonomic neuropathy results in impairment of microvascular thermoregulation and anhidrosis, which results in exceedingly dry skin [25]. Fissuring commonly occurs, and these breaks in the skin are quite susceptible to bacterial invasion with subsequent infection.

Peripheral vascular disease is also a major cause of limb loss in the patient with diabetes [5,13,26]. Typical occlusive lesions in persons with diabetes tend to involve not only the femoral-popliteal segment, but characteristically affect the tibial arteries below the knee [27]. Pedal arteries are usually spared, making them suitable as outflow vessels for distal bypass procedures [28]. The misconception surrounding “small vessel disease” in the foot as a primary factor in diabetic foot pathology has been refuted, while recognizing the importance of functional abnormalities of capillaries and peripheral neuropathy in the etiology of ulceration [27].

Experience with distal vascular reconstruction to restore pulsatile flow to infected, ischemic feet has been quite rewarding in recent years and has led to significant reductions in the incidence of major LEA [19,28]. Accordingly, no diabetic patient should undergo major amputation for serious foot infection without preliminary vascular consultation and arteriography, regardless of age [19].

Immunopathy

Immunopathy and associated defects in leukocyte function have been implicated in the diabetic patient’s inherent susceptibility to infection [20,29–31]. Leukocyte phagocytosis has been found to be significantly reduced in patients with poorly controlled diabetes, and upon correction of hyperglycemia, microbiocidal rates improve [29]. Neutrophil dysfunction also impairs intracellular killing of bacteria, although it is not always correlated with improved function in a euglycemic state [30]. Poor granuloma formation, impaired wound healing, and deficient white cell chemotaxis and adherence have also been attributed to the diabetic state with obvious implications regarding the handling of infections in these individuals [20,31].

Several studies have also reported an inadequate leukocytic response to severe foot infection, a clinical finding that can be found in up to 50% of such patients with diabetes [12,32]. Such perturbations might benefit from administration of granulocyte colony-stimulating factor, although any improvements in leukocyte function or production do not always have measurable effects on clinical outcomes [33,34]. Generally, patients with diabetes tolerate infection poorly, infection adversely affects diabetes control, and uncontrolled diabetes adversely affects the host’s response to the infection [1].

Microbiology

Polymicrobial involvement is the rule in severe diabetic foot infections, whereas mild infections are often monomicrobial. Gram-positive cocci predominate in most infections, but gram-negative rods and anaerobic organisms are also frequently isolated from deeper or limb-threatening infections [7,21,35–40]. In the latter circumstances, 3 to 5 organisms can often be cultured. As indicated, the most common organisms cultured are the aerobic gram-positive cocci. The most frequent isolates in this group are usually *Staphylococcus aureus*, followed by coagulase-negative staphylococci and group B streptococci. Methicillin-resistant *S aureus* (MRSA) has become increasingly prevalent in diabetic foot wounds [41,42]. In a recent study from the United Kingdom, MRSA was isolated from 30% of all ulcers cultured [42]. This represented a 100% increase from a similar study performed by this group just 3 years previously. The earlier investigation also suggested that MRSA colonization was related to prior antibiotic usage and had an

Table 1
Percent frequency of selected bacterial isolates from diabetic foot infections

Organism	Investigator (no. of patients)						
	Ge (730)	Sapico (32)	Gibbons (100)	Wheat (54)	Calhoun (850)	Scher (65)	Grayson (96)
<i>Staphylococcus aureus</i>	42	25	54	37	45.9	35.4	54
<i>Staphylococcus coagulase-negative</i>	25	9.3	32	32	22.6	27.7	12
<i>Enterococcus</i>	29	40.6	32	27	28.7	NA	28
<i>Proteus species</i>	8	28.1	22	17	26.1	55.8	9
<i>Pseudomonas</i>	8	15.6	14	7	15.9	23.1	8
<i>Bacteroides</i>	4	67	67	33	15.6	84.6	30

NA = not applicable.

adverse effect on wound healing [41]. Furthermore, both methicillin-sensitive *S aureus* (MSSA) as well as MRSA have been linked with an increased risk of death [43,44].

Enterococcus is often encountered as well and can become a significant pathogen in this patient population, even though its exact role is still in dispute [20,38]. A recent report of microbiological profiles of 825 infected diabetic foot ulcers indicated that *Enterococcus faecalis* was found in 29% of all wounds [45]. *Corynebacterium* species, commonly known as diphtheroids, are also frequently cultured and are often considered as normal skin flora. However, their frequency in diabetic foot infections suggests that they may represent simple overgrowths of resistant bacterial strains or hold some pathogenicity in the diabetic host [46]. In the previously cited study, *Corynebacterium* species were present in 12% of patients with positive cultures [45].

Aerobic gram-negative pathogens most frequently cultured include *Proteus species*, *Escherichia coli*, and other various species of Enterobacteriaceae [21,36,47,48]. *Pseudomonas aeruginosa* is not as frequently isolated in these infections, despite its ubiquity and the attention it often receives. It is recovered in approximately 10% to 20% of cultures taken, and its prevalence in some wounds has been attributed to prior antimicrobial use [36,45,47,49-51]. One study from India also reported increased healing times in those ulcers infected with *Pseudomonas species* resulting from patterns of antimicrobial resistance [51].

Anaerobic organisms, although rarely occurring in pure culture, can be recovered in as many as 80% of patients with severe infections [40,50,51]. *Bacteroides species* are the major pathogens in this group, although peptostreptococci can be recovered in high numbers [40,49]. Bacterial synergism may be an important determinant of the pathogenicity of *Bacteroides fragilis* in diabetic infections because it has been shown to have increased activity in the presence of enterococci [52]. Anaerobic pathogens have also been linked to longer healing times and to increasing severity of diabetic foot wounds [51].

Culturing wounds that are not clinically infected is generally not recommended [19,38,53-55]. There is generally poor concordance between cultures of superficial exudates or sinus tracts and deep tissue cultures [20,56,57]. Sapico et

al [56] have demonstrated that better concordance is obtained when cultures are taken from a curettage of the ulcer base. Recent evidence suggests, however, that initial swab cultures of limb-threatening infections are as reliable as deep-tissue cultures in identifying underlying pathogens [58]. However, this does not hold true several weeks after treatment, where the latter method may give better diagnostic sensitivity. Table 1 shows the relative frequency of the more common bacterial pathogens isolated from several important studies indicating the variability in prevalence of each organism.

Clinical presentation (classification)

Foot infection in diabetic patients is most frequently a sequela to neuropathic or neuroischemic foot ulceration [6,7,12,20,38]. The open lesion allows entry of microbes that flourish in the presence of an impaired host response [1,38,53]. In patients with vascular insufficiency, the infection rapidly progresses and can quickly evolve into a limb- or life-threatening situation. Because of the neuropathic patients' loss of protective sensation, the emergent nature of an evolving foot infection can go unrecognized until it is too late to save the foot without partial amputation. One study from Sweden reported that approximately half of all patients with diabetes who had deep foot infections associated with an ulcer required amputation before healing or death [12]. Therefore, early diagnosis and appropriate management of evolving foot infections is critical in arresting their progression to more severe degrees of tissue loss.

Systemic signs of toxicity, such as leukocytosis, fever, or chills, can frequently be absent or appear late in the course of a diabetic foot infection [1,12,32,35]. Pain is frequently absent in neuropathic patients and is an unreliable indicator of infection, although patients with deep or serious foot infections often complain of flulike symptoms ("diabetic foot flu"). Recalcitrant hyperglycemia might be the only associated clinical finding indicating the potential severity of an underlying infection [1,7,19]. Therefore, when leukocytosis, fever, malaise, and extreme hyperglycemia are indeed present in patients with foot infections, the infection

should be considered a serious or limb-threatening event [7].

Foot infections have been classified on the basis of severity, extent or depth of involvement, clinical characteristics, anatomic location, and etiology [1,7,20,38]. Ideally, classification of foot wounds and/or infections can facilitate and direct treatment as well as help monitor progress [53]. Although the Wagner wound classification system is certainly the most widely recognized, others have been proposed that specifically address the important parameters of infection and ischemia when categorizing foot ulcers [59–62]. Although very serious and emergent infections, such as crepitant anaerobic cellulitis, nonclostridial anaerobic myonecrosis, clostridial myonecrosis (gas gangrene), and synergistic necrotizing fasciitis, have been described as distinct types of infections affecting the diabetic foot, their specific clinical characteristics are not easily differentiated [20]. Hence, there is not great clinical utility in using such distinctions other than for recognizing their severity and emergent nature. Patients with such infections present acutely ill and require prompt surgical drainage with varying degrees of debridement depending on the extent of tissue necrosis. Necrotizing fasciitis of the lower extremities, arms, and abdominal wall is an important manifestation in persons with diabetes and has an associated mortality of approximately 40% [63]. This is life-threatening infection, which typically manifests as a rapidly progressive necrosis of the superficial fascia and overlying skin with associated systemic manifestations [64]. Combinations of anaerobic and facultative aerobic streptococci, enterococci, staphylococci, facultative gram-negative bacilli, and obligate anaerobes, including *B fragilis*, are often present concurrently, thus synergistically enhancing their pathogenicity [63].

Any of the aforementioned clinical presentations represent medical emergencies. In general, subcutaneous gas or radiographic evidence of gas in deeper tissues is suggestive of either aerobic gram-negative bacillary or anaerobic infection, whereas gangrene is associated with an increased frequency of mixed infections [21]. Accordingly, the probability of polymicrobial involvement must be considered when determining empiric antimicrobial therapy.

A simpler approach is to categorize infections as mild, moderate, or severe (limb threatening) [1,19,35,38,53]. This simple clinical scheme is less confusing and more readily directs appropriate treatment in that moderately severe infections are obviously more serious and always require hospitalization, whereas patients with mild, superficial infections can usually be managed as outpatients. Mild infections are usually associated with superficial ulcers without bone or deep tissue involvement [1]. Moderate infections might have varying degrees of deep tissue involvement with little necrosis and no systemic toxicity. Severe infections can have extensive or rapidly progressive cellulitis, deep tissue necrosis, bone infection, gangrene, ischemia, and systemic toxicity [38]. Similarly, they can be classified as non–limb-threatening, limb-threatening, or life-threatening

infections [19,35,53]. Most often diabetic foot infections are simply classified into 2 groups, non–limb-threatening and limb-threatening infections, with the understanding that rapidly progressing limb-threatening infections can become life threatening [50,63]. Non–limb-threatening infections, often accompanied by a superficial ulceration, are typically superficial with <2 cm of surrounding cellulitis. These patients do not usually show signs of systemic toxicity and, accordingly, can be carefully managed as outpatients [19,53,65]. When ulceration is present, it should not probe to bone or joint. Conversely, a limb-threatening infection requires immediate hospitalization because of extensive involvement and the variable presence of fever, malaise, leukocytosis, and hyperglycemia [1,7,38]. Fever is not, however, always a reliable indicator of severity because temperatures >100°F might be present in only up to 50% of these patients [12,37,53]. Cellulitis will extend ≥ 2 cm, lymphangitis and edema will often be present, as may bacteremia, and associated ulcerations will probe deeply to bone, joint, or deep fascial compartments. Deep abscesses, gangrene, necrotizing fasciitis, and the other specific types of severe foot infections previously discussed are also included in this group.

Management

The severity of the infection, medical status of the patient, and history of medication allergies will usually guide antibiotic therapy [6,7,38,55]. Initial antimicrobial treatment of diabetic foot infections therefore requires careful consideration of these factors in concert with an understanding of antibiotic spectrums of activity, toxicities, and interactions. Once definitive reliable cultures are reported, initial antibiotic regimens should be revised to narrow the coverage to specific pathogens encountered. Conversely, in the absence of clinical improvement despite coverage for cultured pathogens, the empiric coverage should be broadened or augmented until an appropriate response is achieved. In any case, it is important to realize that antimicrobial therapy alone will rarely suffice in managing most foot infections. Adjunctive management should always include avoidance of weight bearing, drainage and debridement procedures, hyperglycemic control, and management of ischemia [66–68]. When managing non–limb-threatening infections on an outpatient basis, careful follow-up is necessary. When such patients do not show a favorable response or are nonadherent to prescribed treatments, hospitalization must be considered. Equally important, diabetic foot infections should be managed with a multidisciplinary team approach [7,12,67].

As previously indicated, those ulcers that do not show overt signs of infection need not be cultured or treated with antibiotics [19,53,55]. Most available evidence at this time does not support the routine use of antibiotics for uncomplicated ulcers [69,70]. However, long-standing ulcers that

Table 2
Selected empirical antibiotic regimens for mild and non-limb-threatening infections

Oral agents	Topical agents
● Cephalexin	● Silver sulfadiazine
● Cefdinir	● Silver powder, gels
● Amoxicillin-clavulanate	● Mafenide acetate
● Clindamycin	● Ciprofloxacin drops
● Dicloxacillin	● Mupirocin
● Ciprofloxacin, levofloxacin	● Gentamicin
● Trimethoprim-sulfamethoxazole	● Bacitracin
● Linezolid	● Cadexomer iodine

have not shown improvement despite appropriate local care might benefit from a course of culture-directed antibiotic therapy. One small, nonrandomized study from the United Kingdom indicated that noninfected ulcers treated with antibiotics had fewer instances of hospitalization and amputation than those receiving no antimicrobial therapy [71]. This concept, however, requires further confirmatory evidence with larger numbers of subjects before it is embraced, because antimicrobial use is not without adverse effects [38].

Treatment of non-limb-threatening infections

These relatively mild infections are often associated with superficial ulcers and can usually be managed without hospitalization. Persons with underlying critical ischemia or deep infection should not be considered in this category. Most non-limb-threatening infections are primarily monomicrobial, with aerobic gram-positive cocci, such as *S aureus*, *Staphylococcus epidermidis*, and streptococci (including enterococci) predominating [39,63,67,68]. Nevertheless, gram-negative organisms can still be recovered in isolation or in combination with gram-positive cocci.

Treatment of non-limb-threatening infections complicating foot ulcers may initially take place in an outpatient setting [7,53,65,67]. Wound debridement is important because it can reduce the bacterial burden as well as promote more rapid healing [53]. As previously mentioned, cultures should be obtained from a curettage of the ulcer base to obtain a reliable specimen [55,56,68]. After culturing, oral antibiotic therapy can most often be initiated using agents with effective gram-positive coverage (Table 2). A recent study comparing linezolid with ampicillin-sulbactam or amoxicillin-clavulanate for diabetic foot infections found that clinical cure rates were comparable for both agents [39]. The former agent, providing primarily gram-positive cocci coverage, actually had significantly higher clinical cure rates for infected foot ulcers than the latter agent, which also had activity against gram-negative rods as well as anaerobes.

The patient should be reassessed within 48 to 72 hours to

ensure that an adequate response to treatment has been achieved. Antibiotic therapy should subsequently be adjusted according to culture results and the patient's response to treatment [68]. There are several topical agents that can be used adjunctively on the infected wound (eg, silver dressings, silver sulfadiazine cream, mafenide acetate, povidone-iodine solution, ciprofloxacin solution), although no single agent or topical antibiotic has been proven superior [45,55,72]. Appropriate wound care, including debridement and offloading or pressure relief, remains an essential component of care [6,7]. Most importantly, if no improvement is noted, hospitalization for incision and drainage, medical stabilization, and intravenous antibiotics should be considered [66–68]. Table 3 presents the basic management concepts for mild or non-limb-threatening diabetic foot infections.

Treatment of limb-threatening infections

Severe, limb-threatening infections include those with ≥ 2 cm of cellulitis, lymphangitis, deep ulceration or abscess, necrosis, gangrene, osteomyelitis, or critical ischemia [35,53,66,67]. These patients require immediate hospitalization for surgical drainage, metabolic control, and parenteral antibiotic therapy [12,19,66,73]. Fever or systemic signs of infection, including leukocytosis, may not be present in up to 50% of cases because of diabetes-related immunosuppression [12,32]. Nevertheless, many patients indeed present with the classic signs or symptoms of deep infection that would be expected, including chills, loss of appetite, hyperglycemia, and malaise. Because these patients are at a heightened risk of major or minor LEA, even at their initial presentation, it is imperative that prompt, aggressive treatment be instituted immediately [12,19,37,73,74]. Delays in appropriate treatment and referral can result in more proximal levels of amputation being required in 10% of these patients [74].

Upon admission, the patient must be evaluated in terms not only of parameters related to the infection, but also pertaining to those comorbidities commonly associated with diabetes. Renal, cardiovascular, neurologic, nutritional, and hematologic perturbances often coexist and must be optimized in these complicated patients. Accordingly, multidisciplinary management of these patients has been shown to improve outcomes and reduce the rate of lower-limb amputation [12,26,66,67,75,76].

Evaluation of lower extremity infection must be systematic and thorough [7,77]. Unfortunately, this is not always the case. In a 4-year study of acutely infected diabetic foot wounds admitted to a large university teaching hospital, <14% of patients received what was considered to be the minimally acceptable level of evaluation [77]. 60% of patients were not even evaluated for the presence or absence of protective sensation with a simple monofilament. Because an inadequate examination can lead to errors in diag-

Table 3
Management concepts for non-limb-threatening diabetic foot infections

Clinical features	Causative organisms	Diagnostic procedures	Management
Shallow ulcer <2 cm cellulitis	Primarily aerobic gram-positive cocci: <i>Staphylococcus aureus</i> , streptococci, enterococci	Culture of curettage tissue or purulent secretions	Debridement
No deep abscess, necrosis, or gangrene		Plain radiographs	Wound care
No osteomyelitis and no bone exposed or probed	Often monomicrobial, but may also involve gram-negative bacilli	Arterial noninvasive testing as indicated	Offloading
No ischemia			Oral or topical antibiotics
No systemic toxicity			Control diabetes
			Outpatient management
			Follow-up 48 to 72 hr

nosis and treatment, this study highlights the importance of assiduousness in the approach to these high-risk patients.

Wounds must first be probed to ascertain the presence of underlying sinus tracts or abscesses, as well as deep or proximal extension along fascial planes, and to determine whether bones or joints are involved in deep infection. Probing to bone by gently advancing a sterile surgical probe into the depths of the wound has been found to have a positive predictive value of 89% for osteomyelitis in these patients [78]. Some, however, have questioned the utility of this test because of concerns about low prevalence of osteomyelitis and lack of sensitivity [79]. That fact notwithstanding, this simple test can be quickly performed on initial examination and can provide a reliable indication for underlying osteomyelitis [6,50,80]. The size and depth of the wound, location, and extent of necrosis, cellulitis, crepitation, and edema must also be recorded at baseline. Initial deep cultures (aerobic and anaerobic) of purulent drainage or deep tissue can usually be taken at bedside in these frequently neuropathic patients. Gram staining will also provide an early indication for the spectrum of organisms involved. Blood cultures should, of course, be obtained as circumstances warrant.

Palpation for pedal pulses is necessary to determine the adequacy of peripheral arterial circulation. Although the absence of palpable pulses does not unequivocally imply that ischemia is present, further noninvasive arterial testing would be warranted [53]. Arterial segmental Doppler pressures with waveforms, including ankle and toe pressures, will be of value in this regard regardless of the frequency of falsely elevated pressures resulting from medial arterial calcification [19,80]. Transcutaneous oxygen tension measurements can also be a fairly reliable indicator, wherein levels <20 to 25 mm Hg would portend a poorer prognosis for healing [81,82]. Finally, vascular surgical consultation and angiography should be obtained to ultimately determine the need for limb-salvaging revascularization [19,53,80,83].

X-rays should be taken and evaluated for evidence of osteomyelitis or soft tissue gas [7,53]. If gas is identified in the ankle or hindfoot, radiographs of the lower leg should be obtained to assess the extent of the gas formation. Whereas x-rays are very insensitive indicators of acute osteomyelitis, they are fairly specific when classic erosive or lytic changes are present in concert with a positive probe test [84,85].

When plain film images are negative and there is clinical suspicion for underlying osteomyelitis, radionuclide scanning with technetium-99m methylene diphosphonate (“bone scan”) can be highly sensitive for detecting early infection [86,87]. The sensitivity of 3- or 4-phase bone scans usually approaches 90% to 100%, but their usefulness is tempered by the frequency of false-positive results that reduce the specificity to $\leq 50\%$ [84,88–90]. The presence of Charcot arthropathy is especially problematic in diagnosing concurrent osteomyelitis because bone scans will uniformly be positive as a result of excessive bone activity even in chronic stages [20,84,91–93].

Indium-111-labeled leukocyte scans, technetium-99m hexylmethylpropylene amineoxine (HMPAQ)-labeled leukocyte scans, technetium-99m-labeled monoclonal anti-granulocyte antibodies, or other variations of white blood cell scintigraphy are more accurate in diagnosing osteomyelitis in patients with diabetes because of their higher specificity [88–90,93–97]. Although indium-111-labeled leukocytes are relatively specific for sites of bone infection, they can still accumulate in sites with preexisting osteoarthropathy [84,93,95]. This modality also is limited by fairly poor spatial resolution, making anatomic identification somewhat difficult. Therefore, a technique of combining bone scintigraphy with leukocyte scans can have greater accuracy with improved specificity of $\geq 80\%$ for infection even in the setting of Charcot arthropathy [90,93,96,97]. Two recent studies reported specificities for osteomyelitis of 100% even in the presence of osteoarthropathy, with accuracies reported in the range of 83% to 96% [96,97].

Magnetic resonance imaging is considered to be a very sensitive and specific indicator of true bone marrow infection [97–99]. The utility of this modality, despite its cost, rests in its superb spatial resolution and anatomical detail of images provided. Accordingly, not only the presence of osteomyelitis can be ascertained, but the extent of tissue penetration as well. This can be most helpful in operative planning, especially in deep infections where the boundaries of soft tissue infection might not be evident on clinical examination alone. In cases of previous trauma, surgery, or Charcot osteoarthropathy, however, the specificity is often reduced because of noninfectious marrow inflammation [98]. Sensitivity for osteomyelitis in diabetic foot infections

is generally reported in the range of 90% to 100%, whereas specificity is in the range of 80% to 100% [84,98,99].

Surgical management of limb-threatening infections is vital and begins with complete drainage and debridement of necrotic tissue, unroofing all abscessed cavities, and obtaining reliable aerobic and anaerobic tissue cultures [19,50,66,80,100]. In fact, Tan et al [73] report that patients admitted with serious foot infections fared better with aggressive early surgical management than with prolonged medical (conservative) therapy with a delay in surgical intervention. Early surgical debridement or limited partial foot amputation with adjunctive antimicrobial therapy resulted in shorter lengths of stay as well as reduced need for major amputations. This clearly contrasted to those patients who had delays of ≥ 3 days before needed surgery was performed, especially when deep infection was present. In another study, 86% of patients with deep diabetic foot infections required surgery, often including minor amputations, in addition to antibiotics before healing or death [12]. Although patients with limb-threatening infections are often quite ill, their sickness is usually directly related to the severity of their infection. Hence, their recovery, in large measure, depends on the timeliness of operative intervention [7].

In neuropathic patients, initial drainage or debridement procedures can be performed at bedside when circumstances preclude or do not necessitate an urgent trip to the operating room. As always, deep tissue aerobic and anaerobic cultures or swabs of purulent drainage should be taken during such procedures. After thorough debridement, these patients must be kept at bedrest to allow further dependent drainage and reduction of edema. Open amputation (guillotine) of a toe, ray, foot, or leg may be the initial drainage procedure of choice when infection cannot be controlled with less aggressive measures [31,40].

When possible, however, care should be taken to preserve as much of the foot structure as feasible to allow functional weight bearing once the episode has finally resolved [7,19,100]. Multiple debridements or revisions of initial procedures are often necessary depending on the course of the infection. If sepsis continues unabated, wider drainage or resection becomes necessary. As infection comes under control and wounds begin to granulate, wounds can be closed primarily, closed with plastic flaps or grafts, left to heal by secondary intention, or managed with negative pressure dressings [7,100–102]. In many cases, limb salvage is dependent on restoring perfusion to an ischemic foot, but sepsis should be controlled before any attempts at revascularization [19,53,80,83]. Restoration of pulsatile blood flow to the foot by means of extreme distal bypass is often critically important in this regard, with a recent study reporting a 10-year limb salvage rate of 58% [28]. Hyperbaric oxygen therapy is frequently considered as an adjunctive measure to enhance oxygenation of peripheral tissues; however, there is a paucity of clinical trials that support its efficacy [103,104].

Polymicrobial involvement of aerobic gram-positive cocci

and gram-negative bacilli, as well as anaerobic organisms, should be anticipated in patients with limb-threatening infections [38–40,50,63]. It is not unusual to recover 3 to 5 organisms from deep tissue cultures of infected foot wounds, especially in the presence of ischemia and gangrene. Accordingly, empirical antibiotic therapy typically includes broad-spectrum coverage for common isolates from each of the 3 aforementioned bacterial groups [38,63]. Not every possible organism needs to be covered initially, however, because recent evidence suggests that gram-positive cocci often predominate in these infections and that coverage primarily tailored for these organisms can be as clinically effective as broader-spectrum coverage [39]. However, in the most severe limb- or life-threatening infections, empirical broad-spectrum therapy that covers *S aureus*, streptococci, Enterobacteriaceae, and *B fragilis* is recommended [38,50,55,66,68]. Antimicrobial agents useful in this setting include ampicillin-sulbactam, piperacillin-tazobactam, imipenem-cilistatin, ertapenem, fluoroquinolones, and third-generation cephalosporins [37,38,68,105, 106]. In patients with penicillin allergy, clindamycin and a fluoroquinolone, such as levofloxacin or ciprofloxacin, can provide fairly broad-spectrum initial coverage [68,105]. Unfortunately, no single agent covers all possible organisms that might be encountered in diabetic foot infections. Combined therapies are therefore frequently prescribed for more severe infections. Such combinations would specifically target MRSA, enterococci, *Pseudomonas*, and anaerobes if these organisms were not adequately addressed by the primary empirical agent. Vancomycin, linezolid, metronidazole, ceftazidime, or aztreonam might be considered as adjunctive agents in these circumstances. Based on the results of cultures, gram stains, and/or clinical response to empirical therapy, antibiotic treatment should be adjusted accordingly. Table 4 lists several antibiotic regimens that might be used in the management of limb- or life-threatening diabetic foot infections. Obviously, the duration of therapy and the length of hospital stay depend on infection severity, clinical response, the need for surgical intervention, and the presence of underlying osteomyelitis [14,37,66,68]. When skilled placement or outpatient intravenous antibiotic therapy is not an option, recent evidence supports the efficacy of initial parenteral therapy with either an aminopenicillin or a fluoroquinolone followed by the appropriate oral agent in the management of these patients [106]. Linezolid therapy also is effective in this regard and can be initially administered by either the parenteral or oral route [39].

Management of osteomyelitis

Osteomyelitis is frequently associated with moderate to severe diabetic foot infections and complicates management [12,37,84,85,107]. In a series of 2,000 foot infections, Calhoun and Mader [107] noted that osteomyelitis was the most common clinical presentation. In a report of an antibiotic clinical trial for diabetic foot infections, 59 of 96 patients (61%) had underlying osteomyelitis [37]. An earlier

Table 4
Selected empirical antibiotic regimens for severe and limb-threatening infections*

Severe	Life-threatening
<ul style="list-style-type: none"> ● Ampicillin-sulbactam ● Linezolid + levofloxacin ● Piperacillin-tazobactam ● Ertapenem ● Cefotaxime, ceftizoxime ● Aztreonam + clindamycin ● Ciprofloxacin + clindamycin ● Vancomycin + ceftazidime ● Linezolid + aztreonam 	<ul style="list-style-type: none"> ● Ampicillin-sulbactam + linezolid ● Ceftazidime + vancomycin + metronidazole ● Piperacillin-tazobactam + vancomycin ● Imepenem-cilistatin ● Linezolid + aztreonam + metronidazole ● Ciprofloxacin + vancomycin + metronidazole ● Linezolid + imepenem-cilistatin

* Most agents initially administered intravenously. Fluoroquinolones and linezolid can initially be given orally when indicated.

study by Newman et al [89] found that osteomyelitis was present in 68% of the foot ulcers studied, although histopathologic confirmation was not obtained in all cases. These findings are important because the presence of bone or joint infection in association with deep foot infection in the patient with diabetes frequently necessitates local aggressive debridement, resection, or partial foot amputation [7,12,14,37,85,107].

Although many studies report on the prevalence of osteomyelitis complicating foot infections, the frequency is often based on clinical response or imaging studies rather than histopathologic diagnosis in concert with reliable bone culture [84]. Surrogate markers for the disease or its cure obscure the true prevalence of this complication in many

series. The 2 necessary studies should have positive findings, including necrosis, chronic inflammatory infiltrates, and positive isolation of bacteria to diagnose osteomyelitis [84,108]. As previously mentioned, a simple clinical guide to the presence of osteomyelitis is either direct exposure of bone or a positive “probe to bone” test [78,89]. Nonetheless, false-positive and false-negative tests do occur and must be appropriately considered with other diagnostic tests in determining subsequent management.

In addition to antimicrobial therapy, resection of infected bone with or without local amputation is the most expedient management for osteomyelitis [12,47,66,80,84,85,109]. Lipsky reviewed the results of several studies that treated osteomyelitis with conservative therapy either alone or in

Table 5
Management concepts for severe and limb-threatening diabetic foot infections

Clinical features	Causative organisms	Diagnostic procedures	Management
≥2 cm cellulitis	Polymicrobial infection with mixed aerobic gram-positive cocci (<i>Staphylococcus aureus</i> , coagulase-negative <i>staphylococci</i> , <i>streptococci</i> , and <i>enterococci</i>); gram-negative bacilli, including enterobacteriaceae and possibly <i>Pseudomonas</i> ; anaerobic cocci and bacilli, including <i>Bacteroides</i> , <i>Peptostreptococcus</i>	Culture of deep tissue, bone, or purulent secretions (aerobic and anaerobic)	Hospitalization
Deep ulcer with abscess, fasciitis, necrosis, or gangrene		Blood cultures as needed	Multidisciplinary care Medical management
±Osteomyelitis and/or septic arthritis		Plain radiographs: nuclear scintigraphy or MRI as needed	Surgical debridement, drainage, initial open amputation, bone biopsy
±Ischemia (nonpalpable pulses)		Arterial noninvasive testing: Doppler pressures, transcutaneous oxygen tension, and angiography as needed	Wound care
Systemic toxicity may be present		Laboratory tests: CBC, ESR, renal panel, etc	Bedrest Empirical broad-spectrum antibiotics pending final culture. Duration depends on severity and extent of osteomyelitis
Loss of metabolic control			Revascularization as needed. Definitive bone resections, amputations, foot-sparing reconstructive procedures Appropriate footwear and surveillance when healed

CBC = complete blood cell count; ESR = erythrocyte sedimentation rate; MRI = magnetic resonance imaging.

conjunction with some type of surgical intervention [84]. Because the results were quite varied and there seemed to be greater benefit with combined limited resection and antibiotics, the latter approach was recommended. However, there are several authors who report fairly high success rates (63% to 77%) in managing osteomyelitis in such patients with prolonged conservative antibiotic therapy alone [110,111]. This question still requires further study with rigorous comparative prospective trials that would ensure accurate diagnosis of bone infection at enrollment.

When the affected bone has been completely resected or amputated, the wound may be treated as a soft tissue infection until inflammation and drainage cease [19,35,65–67]. However, if residual bone is present in the wound, the patient will likely require 6 to 12 weeks of antibiotic therapy based on the culture results [50,110–112]. Parenteral or oral agents may be used, often in combination, depending on the microbial isolates and the infection severity [84,106,110,111]. Antibiotic-impregnated polymethylmethacrylate beads or absorbable calcium sulfate pellets have been advocated for adjunctive treatment of osteomyelitis, and they have become more accepted in recent years [12,113–115]. These antibiotic depot devices can be temporarily implanted after bone debridement and wound closure to deliver very high local tissue levels of the antibiotic without concern for systemic toxicities [47]. Typically, gentamicin, tobramycin, or vancomycin are the agents most often used in the beads. When nonabsorbable bone cement beads are used, they are usually removed in 2 to 4 weeks. The absorbable beads obviously do not have this disadvantage, although the wounds can “leak” some of the calcium sulfate for several weeks while they are being absorbed [114]. Further research needs to be done, however, before these antibiotic delivery devices will be widely accepted as an adjunctive therapy for the management of osteomyelitis. Table 5 presents an overview of the basic management principles for severe and limb-threatening infections.

Summary

Management of diabetic foot infections requires a thorough knowledge of the multiple factors involved, including the relevant microbiological characteristics of these infections. Equally important, the practitioner must maintain a current understanding of appropriate diagnostic and treatment protocols. Because no one specific antibiotic regimen will always be appropriate, management of the infected diabetic foot usually requires a combination of therapies. Typically, these include a variety of antimicrobial agents in concert with surgical drainage, debridement, or osseous resection. Because these patients frequently have numerous medical comorbidities attendant with their diabetes, care is best delivered through a multidisciplinary approach with a focus on limb preservation.

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