Osteomyelitis of the Foot in Diabetic Patients

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Osteomyelitis of the foot, a common and serious problem in diabetic patients, results from diabetes complications, especially peripheral neuropathy. Infection generally develops by spread of contiguous soft-tissue infection to underlying bone. The major diagnostic difficulty in diabetic patients is distinguishing bone infection from noninfectious neuropathic bony lesions. Certain clinical signs suggest osteomyelitis, but imaging tests are usually needed. The $^{111}$In-labeled leukocyte scan and magnetic resonance imaging are the most diagnostically useful. *Staphylococcus aureus* is the most common etiologic agent, followed by other aerobic gram-positive cocci. Aerobic gram-negative bacilli and anaerobes are occasionally isolated, often in mixed infections. Antimicrobial therapy is best directed by cultures of the infected bone, obtained percutaneously or at surgery. Antibiotic therapy should usually be given parenterally, at least initially, and continued for at least 6 weeks. Surgical debridement or resection of the infected bone, when feasible, improves the outcome. With appropriate therapy most cases of osteomyelitis can be successfully managed.

Foot infections and their sequelae are among the most common and severe complications of diabetes mellitus [1–3]. In Great Britain, for example, more hospitalizations for diabetic patients are for foot disorders than for all other diabetic complications combined [4]. Similarly, foot infections are a major contributing factor to diabetes being the leading cause of lower-extremity amputations in the United States [5, 6]. Recent data from Germany also show that 72% of nontraumatic lower-extremity amputations are attributable to diabetes, an increase in risk of 22-fold compared with the risk for nondiabetic persons [7]. In most reported series, about a third of diabetic patients who present with foot infections are found to have evidence of osteomyelitis [1]. In one selected population with diabetic foot ulcers, thorough investigation revealed osteomyelitis in two-thirds of the patients [8].

Foot bone osteomyelitis in diabetic patients is largely a consequence of several complications of diabetes, especially neuropathy, and to a lesser degree vasculopathy and poorly defined defects in immunity and wound healing. Although diabetic foot osteomyelitis has been well-described for over 25 years, little information has been available to assist the clinician in diagnosing and treating these difficult infections. Fortunately, several recent studies have provided data on which to make scientifically base decisions about the care of diabetic foot infections. In fact, in his insightful 1996 review of bone and joint infections, Norden ranked improved outcome of lower-extremity soft-tissue and bone infections in diabetic patients among the most important recent advances [9].

Classification

Although bone infections of the feet in diabetic patients are called osteomyelitis, this in fact is a misnomer. Infection first affects the cortex of the bone, causing what would more properly be called osteitis. As it progresses it can involve the medullary cavity, i.e., become osteomyelitis, but most of the small bones of the foot actually have little marrow.

Two main classification schemes are commonly used for osteomyelitis. That proposed by Waldvogel and colleagues [10] broadly divides infections into those that are a consequence of hematogenous infection of the bone and those resulting from spread to the bone from a contiguous focus. Contiguous infections are subdivided into those with and without vascular insufficiency. These infections are further characterized into acute or chronic osteomyelitis. Chronic infections typically have an insidious presentation, involve necrotic or ischemic bone and surrounding soft tissue, and follow a refractory course. Almost all diabetic patients with lower-extremity osteomyelitis have chronic contiguous infections, usually associated with vasculopathy.

An alternative classification scheme has been proposed by Cierny and Mader [11, 12]. This system combines anatomic disease types and physiological host categories (local and systemic factors) to define 12 clinical stages of osteomyelitis. Most diabetic foot osteomyelitis cases would be classified as 2Bsl: stage 2 (superficial), B (physiologically compromised host), s (systemic compromise [i.e., diabetes mellitus]), and l (local compromise [i.e., neuropathy or vasculopathy]). Longstanding or particularly severe infections can progress to local (stage 3) or diffuse (stage 4) osteomyelitis.

Pathophysiology

While diminished arterial blood supply has traditionally been considered to be the major factor predisposing diabetic patients...
to osteomyelitis, recent observations suggest that neuropathy is a more important factor. Neuropathy occurring as a consequence of the metabolic derangements of diabetes is present in >80% of patients with foot disease [3]. It causes pedal problems in three main ways. The most obvious is that patients with decreased sensation can suffer mechanical or thermal injuries without their awareness, leading to skin ulcerations. Furthermore, motor neuropathy affecting the intrinsic muscles of the foot predisposes to gait disturbances and foot deformities, such as hammer-and-claw toes [1]. These anatomic alterations lead to a maldistribution of weight on the foot, with elevated focal pressure and consequent skin ulceration. They also allow for pressure and trauma to areas of the foot that contact footwear.

Finally, autonomic neuropathy also contributes by interfering with sweating and causing dry, cracked skin. These breaches in the integrity of the skin envelope allow entry of microorganisms, which leads to the soft-tissue infections that serve as the contiguous focus for bone infections. Thus, soft-tissue infection, osteitis, and osteomyelitis are on a continuum, and it may be difficult to discern where in that pathophysiological sequence a particular infection should be classified.

Other factors also play a role in predisposing to foot infections. Superficial fungal skin infections are common in diabetic patients and they, too, allow entry of bacteria through macerated or broken skin. Furthermore, diabetic patients have a higher rate of nasal and skin colonization with Staphylococcus aureus [13]. This virulent pathogen is thus more likely to be present on the skin and take advantage of any disruptions. Diabetic patients also have poorly characterized defects in host immunity that make them more susceptible to certain types of infections [14], including bacterial infections of the skin and soft tissue. Finally, wound healing in diabetic patients is impaired [15]. When an ulceration occurs, healing is often delayed, giving microbial pathogens a longer period of time to establish an infection.

Diagnosis

Diagnosing osteomyelitis in a diabetic patient with a foot infection is difficult [16]. Major problems include differentiating soft-tissue infection from bone infection and infectious from noninfectious bone disorders. Early in the infectious process the signs and symptoms of osteomyelitis may be subtle and no different from those of any accompanying soft-tissue infection. There may be no changes on plain films. When bony abnormalities are apparent radiographically, they may be indistinguishable from those seen with noninfectious destructive lesions that occur in patients with a peripheral neuropathy. This neuropathic osteoarthropathy, often called Charcot’s changes or diabetic osteopathy, is believed to be caused by repetitive trauma and reflex alterations in the circulation of the foot caused by severe neuropathy [2].

In the western world diabetes is the most common cause of this noninfectious osteopathy, and the foot is the commonest anatomic site [17]. The radiological changes that occur with this disorder include fractures, bone destruction, resorption, sclerosis, and periosteal new bone formation [17, 18]. Some studies have found that about half of diabetic patients with clinical findings suggestive of osteomyelitis in fact have osteopathy [19, 20]. Thus, it is important to carefully evaluate patients with diabetic foot infections to determine which require antimicrobial therapy for osteomyelitis.

Clinical evaluation. The first approach to diagnosis is clinical evaluation. Although the history and physical examination are minimally helpful in diagnosing osteomyelitis, some points are worth noting. Patients with soft-tissue infections or skin ulcerations that have been present for more than a week or two, especially if they are located over a bony prominence, are at high risk for contiguous bone involvement. Patients who have previously had osteomyelitis are probably more likely to have another episode, as are those with a history of other foot complications related to peripheral neuropathy. Most patients with diabetic foot infection are not febrile, and they may not even have signs of inflammation of the overlying ulcer [21].

Two clinical findings have been shown to be predictive of the presence of osteomyelitis. First, the larger and deeper the skin ulceration, the more likely the underlying bone will be infected. Newman and colleagues found that an ulcer area >2 cm² had a sensitivity of 56% and a specificity of 92% in diagnosing osteomyelitis [8]. Similarly, deeper ulcers (i.e., >3 mm) were significantly more likely to overlie osteomyelitis than were shallow ulcers (82% vs. 33%). All of the ulcers in which bone was exposed, either visibly or by probing, had underlying osteomyelitis [8]. Grayson and colleagues at the New England Deaconess Hospital (Boston) have shown that bone infection in the depths of a pedal ulcer can be accurately identified by gently probing the ulcer base with a sterile blunt probe [22]. Contacting a bony surface constitutes a positive probe-to-bone test, which they found to have a sensitivity of 66%, a specificity of 85%, and a positive predictive value of 89% in 75 hospitalized diabetic patients with infected foot ulcers [22]. The negative predictive value of 56% suggests this test cannot adequately exclude osteomyelitis.

The second clinical finding of diagnostic help is the erythrocyte sedimentation rate (ESR). Newman et al. found that the likelihood of osteomyelitis in patients with foot ulcers was greater as the ESR increased, and it was present in 100% of those with an ESR of >70 mm/h [8]. Unfortunately, this finding had a sensitivity of only 28%. Similarly, we have found that an ESR of >40 mm/h was associated with almost a 12-fold increased likelihood of osteomyelitis in a prospectively studied series of patients referred with possible osteomyelitis [19, 20]. Various other blood tests, including the WBC count, have not been shown to be clinically useful in diagnosing osteomyelitis.

Imaging studies. Several imaging studies are available to diagnose osteomyelitis [23] (table 1). Roentgenographic changes are a function of inflammatory hyperemia and secondary deossification. Bony abnormalities related to osteomyelitis are generally not evident on plain films until 10–20 days after
infection, when 40%–70% of the bone has been resorbed [24, 25]. Characteristic acute radiographic findings include focal osteopenia, with lucencies in the cortex or medullary bone. Advanced infection may lead to sequestration of dead, sclerotic bone. Although plain film findings are not pathognomonic for infection, a diagnosis of probable osteomyelitis can be made when classic changes are found in the presence of typical clinical findings [24]. Cross-sectional imaging, i.e., CT scanning, is more sensitive to cortical bone involvement and better detects bone sequestra in chronic or incompletely treated osteomyelitis [24].

Radionuclide bone scanning with $^{99m}$Tc-diphosphonate reflects both osteoblastic activity and skeletal vascularity, rather than anatomic changes. It can thus demonstrate abnormal uptake as long as 2 weeks before abnormalities are seen on plain radiographs [25]. Using a three- or four-phase procedure, with scanning being done at intervals ranging from immediately after injection to 24 hours later, improves the specificity for osteomyelitis. Specificity is poor, however, in the setting of any preexisting osseous condition that causes bone turnover, including neuropathic osteoarthropathy and healing infections [25]. Thus, bone scanning is likely to be helpful only when the suspected osteomyelitis is not superimposed on another process that may cause bone remodeling [26].

Gallium ($^{67}$Ga-citrate) has also been used to image osteomyelitis; it localizes to bone by granulocyte or bacterial uptake [26]. Gallium scans are rarely used now, because when compared directly with $^{111}$In-labeled leukocyte scans in patients with suspected osteomyelitis, the latter are usually superior.

Unlike with bone or gallium scans, $^{111}$In-labeled leukocytes are not incorporated into areas of active bone turnover. Thus, accumulation of labeled leukocytes is relatively specific for infection, especially in situations in which there are other osseous abnormalities [25]. Furthermore, as the infection resolves, the $^{111}$In-labeled leukocyte scan normalizes, making it potentially useful for following the response to therapy.

The major limitation of labeled WBC studies in the foot is that the poor resolution may not allow differentiating infection in the bone from that in adjacent soft tissue [25, 26]. Combining this procedure with a bone scan or $^{99m}$Tc-labeled sulfur colloid study (which localizes to the marrow) can improve specificity.

Studies comparing the indium-labeled leukocyte scans to other imaging tests in diagnosing diabetic foot osteomyelitis suggest it is the most accurate of the radionuclide studies [21, 24–27]. However, it is expensive and time-consuming and requires withdrawal and reinfusion of blood. Several investigational scanning agents, e.g., $^{99m}$Tc-HMPAO-labeled leukocytes, $^{99m}$Tc- or $^{111}$In-labeled antigranulocyte antibodies, and $^{111}$In-labeled human monoclonal IgG, are being tested and may be available soon [21, 25].

MRI, because of its high tissue contrast, is more sensitive than CT scanning for bone marrow and soft-tissue infection [24]. The typical marrow signal changes of osteomyelitis, low T1 and high T2 signals, significantly precede either plain film or CT scan changes. However, these MRI changes can be detected in any process that results in marrow replacement or infiltration, including osteoarthropathy [25].

One advantage of MRI is that it may be useful for following the response of an infection during therapy [23]. The main technical limitation of MRI is the relatively poor resolution for the cortex, which may cause some false-negative results in cases of isolated cortical infection. In most recent studies of patients with clinically suspected osteomyelitis complicating soft-tissue infection of the foot, MRI has performed better than plain radiography, bone scans, gallium scans, or WBC scans [23, 28, 29]. Because of the expense of MRI, however, it may be more cost-effective to use it only in patients with a questionably positive result on another imaging test [23].

Bone culture. The definitive method to diagnose osteomyelitis is by a bone biopsy. The specimen can be obtained at surgery or percutaneously with a biopsy needle such as the osteocut (Bard/Angiomed, Covington, GA). If possible a core of bone is removed; if the bone is liquefied only an aspirate may be obtainable. This procedure is estimated to have a sensitivity of up to 95% and a specificity of 99% [30]. It has the advantage of providing culture and antimicrobial susceptibility results, which can guide the choice of antibiotic therapy.

Many diabetic patients with bone lesions do not require local anesthesia for a percutaneous bone biopsy because they have sensory neuropathy. If lidocaine is needed for the procedure, however, it has no significant effect on the recovery of pathogens [31]. Furthermore, in patients who may have negative cultures as a consequence of already receiving antimicrobials, sampling the bone provides material for a tissue gram stain. Finally, a bone biopsy will also allow histopathologic diagnosis of osteomyelitis. This is based on the presence of necrosis, infiltration with leukocytes or chronic inflammatory cells (e.g., lymphocytes or plasma cells), or other signs of inflammation.

Transcutaneous bone biopsy is a safe procedure, with no major complications reported in the literature [21] or in our experience with >100 cases. Bone biopsy specimens may be contaminated by overlying soft-tissue infection, but a route traversing uninfected tissue can usually be found. Areas of infection in a bone may be focal rather than diffuse and may have relatively few microorganisms; thus osteomyelitis can be missed on biopsy. Accuracy may be maximized by aiming for

### Table 1. Comparison of various imaging studies in identifying foot bone osteomyelitis in diabetic patients.

<table>
<thead>
<tr>
<th>Test modality</th>
<th>Approximate mean (range)</th>
<th>Positive predictive value (%)</th>
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<tbody>
<tr>
<td></td>
<td>Sensitivity (%)</td>
<td>Specificity (%)</td>
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<tr>
<td>Plain radiography</td>
<td>60 (28–93)</td>
<td>66 (50–92)</td>
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<tr>
<td>Technetium$^{99m}$Tc bone scan</td>
<td>86 (68–100)</td>
<td>45 (0–79)</td>
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<tr>
<td>Indium$^{111}$WBC scan</td>
<td>89 (45–100)</td>
<td>78 (29–100)</td>
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<tr>
<td>MRI</td>
<td>99 (29–100)</td>
<td>83 (71–100)</td>
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NOTE. Data are from [16, 21–23]. Comparison is based on 5–8 studies (13–88 patients per study) of each modality.
Figure 1. Suggested approach to diagnostic evaluation and treatment of a diabetic patient with a skin ulceration or a soft-tissue infection of the foot. (*Based on results of bone culture, if available; otherwise, based on results of culture of overlying infected soft tissue. †Based on results of soft-tissue culture.)

the area of greatest activity or destruction on imaging tests under fluoroscopic or CT guidance. A negative bone culture for a patient with clinical and laboratory evidence suggesting osteomyelitis does not necessarily exclude that diagnosis. Because of the high cost of obtaining and processing a bone biopsy specimen (~$800) [16, 30], it should be considered most often when the diagnosis is otherwise in doubt or when the likely causative pathogens cannot be adequately predicted.

A recent decision and cost-effectiveness analysis of diabetic foot infections [16] concluded that noninvasive testing adds significant expense for patients in whom osteomyelitis is suspected and may result in little improvement in health outcomes. The investigators suggested that in nontoxic patients a 10-week course of soft-tissue culture-guided oral antibiotic therapy following surgical debridement may be a better approach.

This article was based on a thorough scrutiny of the available literature by authors well-trained in outcomes research and clinical decision-making. I believe, however, that they did not adequately weigh the strength of results obtained from various centers, and I disagree with some of the assumptions they made, including that all patients needed to be hospitalized and to receive intravenous antibiotic therapy initially. On the basis of my interpretation of the current literature and our clinical experience, we follow an approach to diagnosing osteomyelitis as shown in figure 1.

Microbiology

Because diabetic foot osteomyelitis is usually a consequence of spread from contiguous soft-tissue infection, it would be expected that the etiologic agents in these infections would be similar. This is largely true. In nearly all studies of diabetic foot osteomyelitis, the most common pathogen is S. aureus. Next most frequent are other aerobic gram-positive cocci, followed by various aerobic gram-negative bacilli (table 2). Although fewer bacterial species tend to be isolated from bone infections than from soft-tissue infections, polymicrobial infections are frequent in osteomyelitis. Pseudomonas infections usually occur in patients who have been soaking their foot, or those who have sustained a puncture wound, especially of the calcaneous, and particularly in those wearing rubber-soled shoes [35]. Puncture wound infections in diabetic patients are typically polymicrobial, with anaerobes isolated only infrequently [35].

The role of anaerobic bacteria in diabetic foot osteomyelitis is debated. Among patients with anaerobic osteomyelitis, diabetes is a frequent underlying problem [36]. Although they are relatively frequent isolates in serious soft-tissue infections, anaerobes are less common pathogens in diabetic osteomyelitis, especially in reliably obtained bone specimens. The more severe the infection, however, the more likely anaerobes will be isolated [37].

Anaerobes are also more frequent in infections that are longstanding, that have failed to be eradicated by previous antimicrobial therapy, and that are accompanied by necrotic material or a foul odor [1]. Isolating anaerobic (and other fastidious) bacteria requires proper collection, transportation, and culturing techniques. In a few instances empirical therapy directed against anaerobes may be warranted when anaerobic cultures are unavailable or negative but clinical suspicion is high.

Microorganisms that are often considered contaminants in other settings, e.g., Staphylococcus epidermidis [38] and Corynebacte-
Treatment

Antimicrobial therapy. Osteomyelitis is a difficult infection to treat, largely because of limited blood flow in bone. This is particularly true in diabetic patients, in whom peripheral vascular disease of the lower extremities is so common. Thus, this infection, especially when chronic, is infrequently cured. It can recur years, even decades, after apparently successful therapy. Arresting infection is an appropriate goal, but suppressing the process may be the more feasible outcome [11]. Because relapsing or repeated infections are common in diabetic foot osteomyelitis, surgical resection of the infected bone is often necessary [11]. Selecting an appropriate antibiotic to treat these infections is particularly important because of the prolonged duration of therapy required. One issue that is often raised is the penetration of various antibiotics into bone tissue. Although previously considered an important factor, recent evidence has shown that for most antibiotics the concentrations achieved in bone are similar to those achieved in serum [40, 41]. Thus, other factors should be more important in selecting an antibiotic, e.g., the effectiveness against the expected pathogens, potential for toxicity, and cost.

Therapy with a single antimicrobial agent is sufficient for most bone pathogens [42]. S. aureus is the most frequent pathogen isolated, especially in monomicrobial infections. The greatest experience is with penicillinase-resistant penicillins (e.g., nafcillin, 2 g iv every 4 hours) and cephalosporins (e.g., cefazolin, 2 g iv every 8 hours), and these are appropriate agents in most cases. Staphylococci, especially coagulase-negative species, are often methicillin-resistant [35]; these infections usually require vancomycin therapy (1 g iv every 12 hours), which may be less active than β-lactam antibiotics [41].

Combination therapy with rifampin (600 mg orally once daily) appears to enhance activity against S. aureus infections [41]. Parenteral therapy, preferably for 4–6 weeks, is traditionally recommended. This dictum is mainly based on data from animal experimental models [41] and limited, often anecdotal,
clinical experience. There are no reliable data upon which to determine the optimal duration of antimicrobial therapy or the duration of parenteral therapy necessary before switching to an oral agent [43, 44]. Appropriate oral antibiotics include dicloxacillin (0.5 g–1 g every 6 hours), cephalaxin (0.5 g every 6 hours), and clindamycin (300 mg every 6 hours).

Newer agents with excellent oral bioavailability, especially the fluoroquinolones (e.g., ciprofloxacin, 750 mg orally every 12 hours), achieve high tissue concentrations and have yielded success rates in treatment of osteomyelitis similar to those of parenteral agents [45]. The currently available fluoroquinolones must be used with care because they have minimal activity against obligate anaerobes and are not optimal agents for some aerobic gram-positive cocci.

The outcome of antimicrobial therapy for diabetic foot osteomyelitis depends on the severity of the infection and the appropriateness of the treatment. For the 25 patients in the series Waldvogel et al. reported in 1970 [10], a conservative medical and surgical approach aimed at limb salvage (e.g., incision and drainage, bypass, and endarterectomy surgery) was usually attempted first but was rarely successful. More radical treatment, usually involving amputations, cured most patients, even those whose conservative therapy had failed. This experience led the investigators to suggest that an unsuccessful outcome with conservative therapy should prompt more aggressive surgery rather than prolonged medical management. This viewpoint was widely held for the next 2 decades, and amputations were frequently performed for diabetic foot osteomyelitis, especially cases involving the toes [46, 47].

In 1987, however, Bamberger et al. [32] reported in a review of 51 cases of diabetic foot osteomyelitis that most of the patients responded to antimicrobial therapy and did not need ablative surgery. They found that 27 (53%) of the patients ultimately had clinical resolution at a mean follow-up of 19 months. Among other factors, the use for at least 4 weeks of intravenous antimicrobial therapy active against the isolated pathogens or the use of combined intravenous and oral therapy for 10 weeks predicted a good outcome.

There are a number of problems with this study, including the fact that it was retrospective, that osteomyelitis was substantiated histopathologically in only eight (16%) of the patients, and that a variety of antimicrobial regimens were employed. Nevertheless, based on their results, the authors suggested that for patients without limb-threatening infections or extensive necrosis or gangrene, high-dose intravenous antibiotic therapy should be tried before any ablative procedures. In the same year, Hughes et al. [48] found that among patients with diabetic or ischemic foot osteomyelitis the clinical success rates for therapy with parenteral third-generation cephalosporins ranged from 79%–87% at 1 year of follow-up.

In 1987 Nix et al. [49] reported the first series of patients treated entirely with oral antibiotic therapy alone. They found that 19 (79%) of 24 diabetic patients with osteomyelitis were successfully treated without the need for subsequent amputation. Similarly, Peterson et al. [50] reported that among 29 patients with osteomyelitis who received oral ciprofloxacin, 19 (66%) had a successful long-term outcome, i.e., they did not require amputation or rehospitalization for the initial infection for at least a year. These patients received an average daily dose of ciprofloxacin of 1.5–2.0 g for 3 months. An interesting observation from this study was that for the patients whose wounds were closed at the cessation of antibiotic therapy the rate of successful outcomes at 1 year was significantly better than that for those whose wounds remained open (93% vs. 43%; $P < .01$).

We have just reported the results of a multicenter trial of antibiotic therapy for diabetic foot infections [51]. Either ofloxacin or a broad-spectrum aminopenicillin regimen was given parenterally initially (for an average of 7.5 days) and then orally (for an average of 12.6 days). We found that 21 (24%) of 88 evaluable patients had evidence of osteomyelitis. At the end of therapy 11 (73%) of the 15 patients who underwent bone debridement and 4 (67%) of the 6 who did not were cured or improved. Unfortunately, no long-term follow-up was available on these patients. However, we have previously followed a group of 20 patients with biopsy-proven osteomyelitis treated with antimicrobial therapy alone for a mean of 6.5 months. At follow-up, 10% of the patients had died, and the infection healed without recurrence in 25%; a resection of the infected bone was required in 65% of these patients, at an average of 3 months after their evaluation [19, 20].

Karchmer and Gibbons [2] reported their experience at the New England Deaconess Hospital with 18 evaluable osteomyelitis patients treated with prolonged antibiotic therapy. Among the 12 with hind-foot (calcaneal) infection, 7 were cured with “piecemeal debridement,” while 4 required amputation. All of those who required amputation, but none of those who did not, lacked a palpable pedal pulse. Among the 7 patients with forefoot or midfoot infections, 5 underwent limited foot-salvaging surgery and 2 had a foot amputation.

More recently, Gibbons and Habershaw [52] published the results of a trial of broad-spectrum parenteral antibiotic therapy administered for 2 weeks for limb-threatening infections. Of the 95 evaluable patients, 59 (62%) had osteomyelitis. Fourteen patients failed to respond to treatment, of whom 11 (79%) had osteomyelitis. Moreover, at follow-up ~1 year later, 70% of the patients who had a recurrence of infection were those who had had osteomyelitis. Osteomyelitis was not, however, associated with failure to eliminate soft-tissue infection; in 79% of patients with osteomyelitis, compared with 92% of those without concomitant osteomyelitis, the soft-tissue infection was resolved at the end of therapy.

Furthermore, of those with osteomyelitis who were initially cured of soft-tissue infection, 69% had a long-term cure with just 2 weeks of antibiotic therapy. This was attributed to the aggressive ablative surgical debridement employed in this study. Thus, it appears that antimicrobial therapy, especially if given parenterally for at least 1 week and for a total duration of at least 2 weeks, and if combined with debridement of infected bone, can cure many if not most cases of diabetic foot osteomyelitis.
In selecting a specific antimicrobial agent for treatment of osteomyelitis, there are few studies upon which to base a decision. Certainly therapy should be guided by results of aerobic and anaerobic culture and susceptibility tests if possible. A bone culture is optimal; if bone is unavailable, therapy must be based on results of cultures of overlying soft tissues. Whether all isolated microorganisms from a polymicrobial infection require targeted therapy is a debated issue. In his thoughtful recent review of diabetic foot infections, Gerding [37] concludes that in the selection of antimicrobial therapy for osteomyelitis the susceptibilities of all isolated species should be considered. When a bone culture is not available, one must rely on the results of soft-tissue cultures and knowledge of the pathogens usually isolated in these infections.

In these instances, virtually all patients should at least receive therapy effective against S. aureus and other aerobic gram-positive cocci. Expanding therapy to cover aerobic gram-negative bacilli, anaerobic organisms, or both should be considered individually in each case. If indicated, this could be accomplished with a broad-spectrum single agent (e.g., imipenem/ cilastin, 0.5 g iv every 6 hours) or combinations of agents (e.g., aztreonam, 2 g iv every 8 hours, plus clindamycin, 600 mg iv every 6 hours).

**Surgery.** As with other forms of nonhematogenous osteomyelitis, removal of the infected bone is the surest way to ensure long-term eradication. If the infected bone can be easily resected without compromising the integrity of the foot, this is often preferable to prolonged antibiotic therapy that has a substantial chance of failure. When the infection involves a digit, especially other than the great toe, amputation may be the most cost-effective approach [46]. Amputation is certainly appropriate for patients for whom there is no acceptable antimicrobial regimen, whose infection has already destroyed the foot architecture, or who would be better off with a good prosthesis than a foot that is persistently ulcerated or infected [1].

One advantage of resection of all infected bone is that antimicrobial therapy can then be focused on the residual soft-tissue infection [2]. When a major amputation or complex surgery in an ischemic limb would be needed, however, surgery should be avoided, if possible. Gibbons and others believe that there is no cost-benefit to performing a primary major amputation rather than pursuing an aggressive approach to limb salvage [53].

Recent data show that an aggressive surgical approach for cases of osteomyelitis involving infected bone with areas of devitalization and necrosis may allow foot-sparing resections. Karchmer and Gibbons reviewed their experience at the New England Deaconess Hospital with 110 patients with histopathologically confirmed pedal osteomyelitis [2]. Among 86 patients with infection involving the phalanges or metatarsal heads, 76 (88%) were cured by a combined limited surgical procedure, i.e., resection of a toe or ray or a transmetatarsal amputation. This approach left a weight-bearing surface in all patients and allowed antibiotic therapy to be limited to an average of only ~2 weeks.

The level of amputation depends on several factors, especially the vascular status of the limb and the functional needs of the patient. Critical ischemia of the lower extremity, which may be unrecognized, is associated with poor healing of ulcerations and the need for amputations [2, 54, 55]. Clinical judgment, noninvasive tests (including measurement of transcutaneous oxygen levels), and ultimately angiography may be necessary to assess the blood supply to the affected limb. An aggressive approach to arterial reconstruction may allow more thorough drainage and debridement of infected soft tissue and bone. In skilled and experienced hands, vascular reconstructive and bypass procedures have improved limb-salvage rates in these patients [2, 56].

A recently published retrospective review of 112 patients with diabetic foot infections, 65 (58%) of whom had osteomyelitis, addressed the issue of the effect of early and aggressive surgical intervention [34]. Tan and colleagues reviewed the records of 77 patients who underwent prompt surgical intervention, including either debridement or local limited amputation, and 87 patients who had no surgery during the first 3 days of hospitalization. For the whole group of patients the outcome was not correlated with the microorganism isolated, the bacterial susceptibility pattern, or the antimicrobial agent used. Patients who had early surgical intervention vs. those who did not, however, had a significantly lower rate of subsequent above-ankle amputation (13% vs. 28%) and a shorter duration of hospitalization (9.6 days vs. 18.8 days). The authors also emphasized that some patients’ conditions may appear less serious or more superficial at presentation than they are found to be at surgical exploration.

**Adjunctive measures.** Many additional measures have been recommended for treating osteomyelitis, including use of various topical agents, electromagnetic and ultrasound treatments, and local antibiotic injections and pneumatic compression boots [57]. Optimizing the patients’ glycemic control and reducing any edema present are helpful adjuncts to therapy. One frequently recommended treatment is hyperbaric oxygen. There have been many anecdotal reports and a few small controlled studies of this modality [58, 59]. Some data suggest that for patients with diabetic foot infections hyperbaric oxygen hastens healing of wounds, improves the outcome of infections, and reduces the need for amputations. Most authorities believe that it has not yet been shown to be sufficiently beneficial to justify its routine use [44, 60], especially considering the expense and practical difficulties of administering the treatment.

**Prognosis and Prevention**

As previously discussed, the short-term outcome of treatment for diabetic foot infections has improved greatly and is now usually favorable. The long-term outlook, however, has been less well-studied. Data from several retrospective investigations have shown a 2-year mortality rate of 35%–50%, with a cumulative amputation rate over 1–3 years of 40% [61]. Apelqvist and colleagues undertook a prospective study of 468
consecutive patients hospitalized because of diabetic foot ulcers whose lesions healed, either primarily or after surgery (including amputations) [61]. Despite the fact that these patients were educated about foot care and were followed regularly by a specialized diabetic foot care team, the incidence of development of another foot ulceration was 61% and the rate of amputation was 22% within the next 3 years. Both of these complications were seen more often in the patients who required an amputation at the time of their index ulcer. These amputation rates are similar to the 35%–42% rates noted by others [61] at 1–3 years after a diabetic foot ulcer. The fact that almost all subsequent amputations were precipitated by a foot ulcer stresses the need for life-long observation and preventive foot care.

The mortality rate among the patients reported by Apelqvist was also high: at 3 years it was 27% for those who had primary healing of the index ulcer and 41% for those who had undergone an amputation [61]. This mortality ratio was two to four times higher than an age- and sex-matched population. Boyko and colleagues have reported similar findings in a population of veterans in the United States [62]. Among 725 diabetic subjects participating in a prospective study of risk factors for lower-extremity complications, 72 died during a mean follow-up period of 691 days. The relative risk of death was 2.4 in the subjects who developed foot ulcers compared with those who did not, and it was still statistically significantly elevated after adjustment for all known confounding variables.

In addition to the morbidity and mortality associated with these diabetic foot problems, Apelqvist and colleagues also determined the financial cost. The average total direct cost (in U.S. 1990 dollars) for patients who healed primarily was $8,500, while for those who required an amputation it was from $43,000 to $65,000 [63]. For the next 3 years the cost per patient was $16,100 for primarily healed patients without critical ischemia and $26,700 for those with critical ischemia [64]. For patients whose ulcer healed after a minor amputation the costs were $43,100, while for those who required a major amputation the costs were $63,100.

Given the severe consequences of foot infections, it is apparent that preventing these infections is a key component of the care of diabetic patients. Several studies [65, 66] have shown that a methodical, multidisciplined approach to foot care can markedly reduce the incidence of foot ulcerations, infections, and amputations, even in those at highest risk. This approach requires involving health care providers, who must educate the patient on all aspects of foot care and examine the patient’s feet on a regular basis. It also requires active participation by the patient, who must learn and apply preventative measures, including caring for the foot skin and nails, wearing proper footwear, striving for optimal diabetic control, avoiding smoking, and having regular health care visits.

References
