Foot Problems in Diabetes: An Overview

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Diabetes is the leading cause of nontraumatic lower-extremity amputations in the United States. Most amputations are preceded by an ulcer, and ulcers are costly in their own right. Most ulcers are neuropathic in etiology and plantar in location. They occur typically at sites of high mechanical loading because of repetitive trauma in people with loss of pain sensation. In an adequately perfused limb, such ulcers are not difficult to heal. When they are properly mechanically off-loaded, ~90% of these wounds heal in ~6 weeks. The reference standard off-loading device is the total contact cast, but other reasonably efficacious methods exist. Screening and implementation of preventive measures in the high-risk patient are highly recommended and can reduce the incidence of ulceration. All patients with diabetes should be screened annually for loss of protective sensation, with the 10-g Semmes-Weinstein monofilament being the easiest tool to use. Education to prevent complications should be implemented for all patients with loss of protective sensation.

More than 50% of nontraumatic lower extremity amputations are performed on patients with diabetes [1], and the relative risk of having a major amputation associated with diabetes in the Medicare population is ~10 [2]. Lower-extremity problems in the diabetic patient had often in the past been referred to as "the forgotten complication," compared with eye disease and nephropathy. Much progress has been made in the last decade in the understanding of diabetes-related foot problems, as evidenced by an increasing number of publications, symposia, and presentations at major meetings in this field. Unfortunately, much of this new knowledge has not yet been adequately translated into clinical practice. A reduction in diabetes-related amputations was a goal of Healthy People 2000 [3], yet despite all of these advances in knowledge, the diabetes-related amputation rate in the United States in the last 10 years has declined, at best, only modestly [4], if at all [3].

Amputations are not only a personal tragedy, but they are also financially expensive. One recent estimate of the direct medical cost of a leg amputation in the United States was $50,000 [5], translating to an annual total cost in the United States of $1.6 billion, and the indirect costs are likely to be many times greater. Most lower-extremity amputations are preceded by skin ulceration [6]. Ulcers are a more common foot complication of diabetes than is amputation, but they are more difficult to account for epidemiologically. A common estimate is that 15% of patients with diabetes will have a foot ulcer at some point in their lives [5]. In addition to being a precursor to amputation, foot ulcers are inherently important. As well as being onerous for the patient, ulcer care is expensive, with one estimate of the annual total cost of direct medical care of diabetes-related foot ulcers in United States being $9 billion [5, 7].

Although infection is the focus of this supplement issue of Clinical Infectious Diseases, the goal of this article is to provide an overall framework of the pathophysiology and treatment of the foot complications of diabetes to put its infectious aspects into full context.

MULTIDISCIPLINARY APPROACH

The statement that diabetes-related foot problems require a multidisciplinary approach is often made, but what does it mean? Without a team approach, specialists often tend to focus only on the specific aspect of the problem for which they have been trained. For
example, the tendency is for the vascular surgeon to see each case as a vascular issue, for the orthopedic or podiatric foot surgeon to see a foot in need of reconstruction or a functional amputation, for the infectious disease specialist to focus on the microbiological etiology and antibiotic selection, for the endocrinologist to want to optimize glucose control, for the nutritionist to concentrate on diet designed to promote glycemic control and wound healing, for the orthotist to see a “footwear patient for life,” and for the Certified Diabetes Educator to see a failure of education. Although all of these may be relevant, mechanical off-loading is central to ulcer healing, and yet it often receives only lip service from all of the disciplines. Herein our goal is to present the truly multidisciplinary nature of the problem. The specific specialty training of the foot-care team leader is less important than his or her interest in and dedication to this difficult and complex problem.

THE ROLE OF NEUROPATHY

Although most patients and many clinicians still believe that diabetes-related foot problems are predominantly vascular in etiology, in reality most foot infections (and amputations) start with a foot ulcer [6], and foot ulcers develop because of loss of protective sensation (LOPS). LOPS is the level of sensory loss that permits skin injury to occur without the process being “adequately” painful (i.e., the person can continue the injurious activity). LOPS is a negative symptom, an absence of something, about which the majority of patients do not complain. Moreover, many patients with LOPS believe that they in fact have normal, or at least adequate, sensation. They may well have some sensation, but it is not good enough to prevent injury. It is thus essential that all patients with diabetes be screened annually for LOPS.

LOPS has been defined by use of a variety of quantitative sensory tests, but the most frequently used are vibration perception and light-touch testing [8]. The conventional tools of electrophysiology (electromyography or nerve conduction velocity studies) are not useful in this diagnosis. Although there is some debate about the relative accuracy of vibration versus light-touch testing [9–11], we believe the 10-g nylon monofilament test for light touch to be the more clinically appropriate because of its remarkable simplicity (figure 1) [8, 11]. The monofilament is pressed against the skin until it buckles and is then held for 1 s and removed. The monofilament should be applied with varied cadence, and the patient, with eyes closed, should indicate when the touch is perceived. It is best to avoid calloused skin. Traditionally, many sites on the foot have been tested, but it is adequate to test the distal plantar regions, where neuropathy is always the most severe. It is useful to have a family member or a friend watch, because their amazement at the absence of feeling helps reinforce the point for the patient. Testing for LOPS should be a part of the annual “30-second foot screening” (table 1) [12].

CAUSES OF FOOT INJURY IN THE SETTING OF LOPS

Once LOPS is present, what are the secondary causes of neuropathic foot injury? Most ulcers develop on the plantar surface [8], usually under the metatarsal heads (figure 2A) or on the toes. As is seen in figure 2B and documented in multiple studies [8], plantar ulcers occur most frequently at sites of high plantar pressure. Skin breakdown does not usually result from a single step on a sharp object, but rather from cumulative (pressure) loading over hours or days on a highly loaded area. The exact mechanical threshold for skin breakdown remains to be determined and is likely to be a complex function of both per-step loading and behavior (i.e., activity level and footwear use).

Most people have areas of relatively high pressure under some metatarsal heads, but those with normal sensation do not ulcerate because their sensory feedback leads them to avoid prolonged excessive loading. In addition to lacking this basic sensory protective mechanism, patients with diabetic neuropathy tend to have higher than normal pressures for a variety of reasons [8], which make their risk much greater. We believe that some neuropathic patients have such high plantar pressures that they can ulcerate after just a few steps barefoot—for example, while standing in the shower. Typically, these are patients with prior foot surgery and severe deformity.
Dorsal ulcers are less common and occur as a consequence of some obvious injury. Most people sometimes wear uncomfortable shoes for special occasions (e.g., for a wedding) but tend to quickly remove them. However, the patient with LOPS can wear those overly tight dancing shoes at a wedding all night, with disastrous consequences. Shoes that do not accommodate existing deformities (such as bunions) can rapidly lead to ulceration.

THE PATH TO AMPUTATION

The pathophysiology of diabetes-related foot problems is summarized in figure 3. Neuropathic foot injury plays a central role. A minority of patients present with gangrene with no skin injury or only a minor precipitating event, with still-normal sensation. These patients typically have pain. More often, however, vascular problems complicate a neuropathic foot ulcer rather than being a primary event. Vascular disease in diabetes is certainly common, but it often becomes a limb-threatening problem only after a skin injury. Foot ulcers or infections cannot heal without adequate circulation. Infection is likewise uncommon without a preceding skin ulcer. However, severe or deep infection due to a neuropathic skin ulcer that cannot be controlled is often the most proximate reason for amputation.

In the setting of LOPS, the contributing factors to ulceration and amputation, summarized in figure 3, take on added importance. We have, therefore, devised the “2-minute foot examination” (table 2) [12] for patients identified as at risk in the 30-s assessment (table 1). Although most clinicians do not have access to equipment to measure plantar pressure, plantar callus has been found to be a reasonable clinical surrogate for predicting ulceration [13]. Hemorrhage into callus, usually referred to as a pre-ulcer, is a key clinical entity, but the serious implications of this lesion frequently go unrecognized by the clinician (figure 4)—there, but for a few more steps, is an ulcer.

THE ULCERATED FOOT AND OFF-LOADING

In the face of a neuropathic ulcerated foot, the expectation, which should be shared by the health care provider and the patient, is that the ulcer will heal. Most wounds in the diabetic foot develop because of unperceived trauma, and most so-called nonhealing wounds are a consequence of that same ongoing trauma. This has been shown in multiple studies of total contact casting [8, 14–16], a method of mechanically protecting a foot ulcer by reducing loading levels to an extremely low level [8]. In addition to adequately off-loading weight from the ulcer, this is also a method that the patient cannot interfere with, even inadvertently, because the device cannot be removed from the foot.

A review [14] of total contact casting found remarkably similar results among the 13 published studies, comprising some 526 ulcers. Ulcers had been present for 182 ± 14 days (mean ± SE), but ∼88% healed in an average of 43 ± 2 days. The small SEs are noteworthy; 11 of the 13 studies had mean healing times of 36–44 days. Although virtually all of these studies used retrospective controls, similar data were obtained in 2 randomized controlled trials of the total contact cast (TCC) [15, 16]. In the study by Armstrong at al. [15], for example, healing by 12 weeks was 89.5%, which translates to an average healing time of ∼6 weeks for the ulcers that healed.

Margolis et al. [17] recently reviewed neuropathic ulcer heal-
ing rates under “usual care,” by examining the control arms of studies in which various new agents for enhancing wound healing were tested (figure 5). Usual care in centers with enough interest to participate in research studies resulted in healing of ∼31% of ulcers by 20 weeks. Note that this is only about one-third of the healing, in twice the time, compared with the typical result of a TCC [15]. Given the remarkable efficacy of the TCC, it is difficult to understand why it is not more widely used for healing neuropathic ulcers and why healing rates of usual care are not better. The high expense, labor intensity, and poor insurance reimbursement may discourage the widespread use of the TCC. Also, many fear the fact that a wound cannot be examined daily in a TCC. Unfortunately, even more expensive and yet less effective treatments, such as the various “active” wound-healing products, are better reimbursed. Pressure-relieving devices that represent alternatives to the TCC do exist and are reviewed elsewhere in this supplement issue of Clinical Infectious Diseases [21]. However, none are as clinically efficacious as the TCC.

**ASSESSMENT OF THE ULCERATED FOOT**

Appropriate assessment of a foot wound is critically important both for determining the course of treatment and for planning a strategy to prevent recurrence.

**Neuropathy.** Before the best means of off-loading is determined, the ulcerated foot must be properly assessed. If the patient has normal protective sensation, and the wound is in fact painful, then some process other than a neuropathic ulceration is present (e.g., ischemia, trauma, malignancy, venous stasis).

**Vascular status.** Assessment of the vascular status begins with palpating for the dorsalis pedis and posterior tibial pulses. Although digital ischemia can occasionally occur in a foot with a readily palpable pulse, the presence of an easily palpable foot pulse almost always indicates good blood supply. If there is a question about whether a pulse is present, we obtain the hallux blood pressure; values of >40–50 mm Hg suggest adequate perfusion. Other screening options include determination of trans-cutaneous partial pressure of oxygen, determination of the ankle brachial index (which may be normal, even in the presence of significant disease, because of medical calcinosis), and Doppler assessment. Feet with bounding pulses and no other clinical evidence of vascular compromise do not require immediate formal vascular testing.

Patients who do have vascular compromise should be referred to a vascular surgeon familiar with the challenges of peripheral arterial disease in diabetes. These patients often have atherosclerotic disease, predominantly of the arteries between the knee and the ankle. Over the last 15 years, arterial bypass techniques from the thigh into the foot have been very successful [22]. Key requirements, however, are an experienced surgeon, adequate preoperative imaging of the foot arteries (standard or MRI angiography and, sometimes, adjunctive ultrasound), and close collaboration with the medical team, because these patients often have many other medical problems. In general, for a patient who could withstand bypass surgery,
Figure 3. Pathways to amputation: loss of protective sensation permits skin injury, which is most commonly at a site of high plantar pressure. Dorsal injury results from shoes that do not fit the foot or foot deformities. Dry skin, particularly on the heel, can cause cracks that can be a portal for infection. A few amputations result from de novo gangrene, but most result from infection, ischemia, or both complicating a neuropathic ulcer.

an amputation should not be done without adequate imaging of the arterial tree.

The once firmly held belief that occlusive microvascular disease in the diabetic foot is the cause of important ischemia has long been discredited [23]. Although the capillary circulation in the skin in diabetic patients is not normal, healing of diabetic neuropathic ulcers is usually prevented by inadequate off-loading and not by microvascular disease. Microvascular disease must not be used as an excuse for poor off-loading.

A commonly raised question in this setting is “What role does hyperbaric oxygen therapy play?” There is no clear evidence of benefit for the well-perfused foot. However, benefit has been suggested for the ischemic foot in several studies [24–27], some controlled and randomized. All were relatively small, with only short-term follow-up, and no studies have directly compared this therapy with revascularization. Revascularization, therefore, remains the standard of care when it is possible, but hyperbaric oxygen therapy should be considered when revascularization of an ischemic foot is not possible.

Infection. When a clinician is faced with a neuropathic foot wound, concerns about infection often predominate. Consequently, it is unusual for a patient with a new foot ulcer to leave the office without a prescription for an antibiotic. Although clinically infected lesions should certainly be treated with antibiotics, there is no support for using them on uninfected wounds (further reviewed by Lipsky [28]). Infection can be a critical event that precedes amputation in many cases, but in the care of an ulcer, other factors, primarily mechanical off-loading of the wound, are often neglected.

As noted, neuropathic wounds can develop infections, which may spread contiguously. The deeply infected foot should be treated as a medical and surgical emergency. In less serious cases, many questions about the role of infection remain (table 3). The most fundamental is determination of the presence or absence of infection, and a related question is the determination of when antibiotics are indicated. We reviewed the treatment of 65 consecutive plantar neuropathic foot ulcers (unpublished observations) that had been present, on average, 4 months prior to presentation to our clinic. We made the clinical decision that an infection was present at some point during the course of therapy in only 24 cases (37%), and only these patients received antibiotics. Although not all were treated with the TCC, all of these lesions healed in an average of 8.2 weeks. Thus, many neuropathic foot wounds heal without antibiotics. Chantelau et al. [29] have suggested that not even all “infected” (by their definition) neuropathic wounds need antibiotics. We have shown that treatment or outcome of non–limb-threatening ulcer-associated cellulitis not previously treated with antibiotics is not altered by obtaining samples for culture; empirical therapy with a simple antibiotic is adequate [30].

Probably the most controversial aspect of infection in a patient with a neuropathic foot ulcer concerns osteomyelitis—specifically, the indications for evaluation, the type of evaluation, and the type of treatment. We believe that in current clinical practice in the United States, radionuclide and MRI evaluation for osteomyelitis are overused and often lead to such problems as unnecessary medical and surgical treatment, antibiotic resistance, and increased cost of care. All of these issues are further addressed in this supplement issue [28, 31].

OTHER FACTORS IN HEALING OF FOOT ULCERS

Debridement. Debridement is believed to play an important role in management of neuropathic ulcers, even though almost no data in the literature address this issue [32]. A few surgeons even recommend complete excision of every foot ulcer in the operating room before starting other treatment [33], thereby converting a chronic to an acute wound, but that approach is unusual. It is well accepted that debridement should consist of
at least removing callus around a wound, any dry eschar, and all necrotic material. This can usually be accomplished at the bedside. It is often recommended that undermined wound edges be eliminated, even though in many cases they do not prevent wound healing. Vascular surgeons generally believe that a gangrenous, dry, blackened surface eschar on an ischemic foot should not be debrided, because this usually results in enlargement of the wound without improved healing if the underlying ischemia is not corrected first.

Wound dressings. Wounds kept moist appear, in general, to heal faster than do wounds allowed to dry [34]. Occluding a wound provides a moist environment and promotes autodebridement [32]. Too much moisture, however, can macerate healthy tissue around the wound; dressings that absorb large amounts of moisture appear to be useful in this setting. Manufacturers do not need randomized controlled trials to be able to put dressings on the market. As the Cochrane group has reported [18, 35], there are very few controlled trials that support the use of any specific type of dressing in any given setting. To our knowledge, no studies have examined the use of different dressings for diabetic foot ulceration. Furthermore, commercial dressings are expensive. This topic is reviewed more completely elsewhere in this supplement [36].

Active wound-healing agents. Another expensive treatment option is the group of biologically active wound-care products that have been introduced in the last few years [17, 19, 20, 37]. The products currently available on the market essentially deliver growth factors to the wound. Becaplermin (Regranex) is recombinant platelet-derived growth factor. Both Apligraf and Dermagraft apply living skin cells (derived from fetal foreskin) to the wound, but both probably act via growth factors secreted by the newly applied cells. These products have been compared with “usual care” (figure 5). All clearly exert a measurable biological effect, but none produce healing results comparable to a TCC; presumably, therefore, off-loading in these studies was suboptimal. Whether these biologically active products can improve healing of an ideally off-loaded wound is unknown. Recently, recombinant human epidermal growth factor was tested in a small study of unusual ulcer patients (the majority of the ulcers were on the toes, and the majority of the patients did not have LOPS) with, again, clear biological effects [38].

**CARE OF THE PATIENT AT RISK**

The typical at-risk patient will exhibit LOPS and/or vascular disease (table 1). Prevention of ulceration in the patient at risk is the goal but is difficult. Among patients with a previous foot ulcer, reulceration rates are as high as 28%–100% over 1–4 years, even in specialized clinics [39–43].

Prevention of neuropathic foot injury is first a matter of patient behavior. Patients who truly understand the relevance of LOPS and develop appropriate behaviors have fewer foot complications. However, formal studies of the psychological, personality, and knowledge factors that predict good outcomes are only now being conducted [44, 45]. Ideally, a health care provider could assess a patient’s psychological profile, personality, and knowledge base and could recommend specific ed-
Foot Problems in Diabetes

Figure 4. Hemorrhage into a callus (arrows), otherwise known as a pre-ulcer, is demonstrated in these two images. These lesions are almost universally not recognized by patients as important, and yet they are an ulcer “but for a few more steps.”

Figure 5. Efficacy of various treatments in healing ulcers. The total contact cast (TCC) heals \( \sim 90\% \) of neuropathic foot ulcers by 12 weeks [15] (which translates to an average healing time of 6 weeks). Margolis et al. [17] concluded that “usual care,” with the data derived primarily from the control arms of the studies of Regranex and Dermagraft, heals \( \sim 31\% \) of ulcers by 20 weeks, whereas the various biologically active treatments are all better than “usual care” but not as good as the TCC [18–21].
Table 3. Infection in the ulcerated foot: some unanswered questions.

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<th>Question</th>
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<tr>
<td>How should infection (as opposed to colonization) be diagnosed?</td>
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<tr>
<td>Once an infection is diagnosed, when and how should culture of samples</td>
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<tr>
<td>from the wound be done?</td>
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<tr>
<td>When should antibiotic therapy be used and for how long?</td>
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<tr>
<td>When should antibiotics be given parenterally, orally, or topically?</td>
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<tr>
<td>How should osteomyelitis be diagnosed?</td>
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<tr>
<td>When and how can osteomyelitis be treated medically, and when is it</td>
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<tr>
<td>necessary to excise infected bone?</td>
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whereas effective shoes distribute them. Shoes must also accommodate nonplanter deformities such as bunions and clawed toes. Beyond that, there must be enough cushioning to protect the plantar surface or enough room in the shoe to add a cushioning insole. Reasonable-quality sports (athletic) shoes are a good starting point for patients without too much deformity; these shoes can reduce plantar pressure by ~30% by virtue of the cushioning inherent to their design. Similar effects can be achieved by placing a thick, soft insole in shoes manufactured with extra depth. Thickness of the insole is very important and should be ≥6 mm and preferably 10 mm, for which there must be adequate room in the shoe. Some insole materials wear out very quickly; an insole that is worn thin is of no use, and neither are hard insoles often used to “correct” functional problems in patients without neuropathy. In addition, an insole can be modified to shift loading away from areas of concern to areas that are not loaded as a rule, such as the arch, by adding insole material proximal to the metatarsal heads. Creating a rigid and rockeried outsole is the most efficacious modification for reducing forefoot plantar loading. Finally, significantly deformed feet require custom-made shoes.

Unfortunately, no precise linkage has been established between foot and patient characteristics and the shoe prescription. As a rule of thumb, patients who are more active, who have significant foot deformity, or who have a prior ulcer and/or plantar calluses will need more-sophisticated footwear (table 4).

In contrast to the conservative approach of using therapeutic footwear, some practitioners believe that the high-risk foot itself should be changed surgically to reduce such problems as prominences and plantar pressure points. Such surgeries would include correction of bunions or clawed toes, metatarsal head resections [8, 49, 50], lengthening of the Achilles tendon [51], and reconstruction of Charcot fractures [52, 53], among others. There are no well-designed studies to guide practice, and invariably the bias and experience of the practitioner are a major factor in the choice of therapy. We take the approach that only the foot that repeatedly ulcerates despite the use of well-designed footwear should be considered for surgery. Other centers are more aggressive at offering therapeutic or even “prophylactic” surgery [8]. Two studies, however, show an unacceptably high incidence of Charcot fractures in patients who have undergone relatively minor surgical procedures in the foot [54, 55].

**SUMMARY**

Care of the patient at risk for diabetes-related foot problems must be truly multidisciplinary. The underlying problem is usually sensory neuropathy, or LOPS. The patient with LOPS must be convinced of the presence of LOPS and its implications for self-care. Such a patient is a “footwear patient for life.” If the patient develops a foot ulcer, care must be urgent and effective; proper off-loading is essential, and healing in the well-perfused foot without major infection should be expected in an average of 6 weeks. Currently available lower-extremity revascularization techniques have revolutionized care of the ischemic ulcerated foot.

Several fundamental aspects of the infectious complications of the ulcerated foot remain to be clarified and are the topic

Table 4. Principles of footwear prescription for the diabetic foot at risk of amputation.

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<thead>
<tr>
<th>Footwear</th>
<th>Modification</th>
<th>Comment</th>
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<tbody>
<tr>
<td>Sports shoe</td>
<td>Can replace supplied insole with flat foam insole</td>
<td>Make sure that there is enough dorsal room for clawed toes</td>
</tr>
<tr>
<td>Extra-depth shoe with 6-mm insole</td>
<td>Often supplied with just a “spacer” insole; this should be replaced with a prescribed flat foam insole</td>
<td>Make sure that there is enough dorsal room for the toes, particularly if thicker insole is used</td>
</tr>
<tr>
<td>Extra-depth shoe with custom insole</td>
<td>Insole may be molded to the foot and will incorporate reliefs and supports to shift load from high-risk areas</td>
<td>Insole will need to be made by a specialist technician, but the mold can be made in the physician’s office</td>
</tr>
<tr>
<td>Extra-depth shoe with custom insole and rigid roller or rocker outsole [8]</td>
<td>Any experienced shoemaker can make the sole rigid and produce a rocker sole</td>
<td>Make sure that the axis of the rocker is behind the metatarsal head of interest</td>
</tr>
<tr>
<td>Custom footwear</td>
<td>This can accommodate any foot deformity; insole can be of any thickness with any modifications and can be made rigid rollered or rockered</td>
<td>This will need to be measured and made by an experienced orthopedic shoe technician</td>
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NOTE. From [12] (used with permission). Shoes are presented in order of sophistication, complexity, and expense. The more active the patient is and the more deformed and at-risk the foot is, the further down the table one should go to select the footwear. Many patients with lack of protective sensation do very well with sport shoes. Medicare and now most insurance programs cover 1 pair of shoes with modifications per year.
of other articles in this supplement. For example, the identification of the subset of patients with ulcers who require antibiotic treatment for ultimate cure is the subject of ongoing controversy and study. It is clear, however, that infection occurs typically only after a neuropathic or ischemic ulcer develops, so it is probable that implementing optimal ulcer prevention and management strategies will reduce the likelihood that infection will occur. Finally, a full understanding of ulcer pathogenesis by the clinician responsible for management of infection will ensure that attention is paid to factors other than antibiotic selection, including the frequently neglected need for adequate pressure off-loading of the wound.

References


