

CLINICAL PRACTICE

Neuropathic Diabetic Foot Ulcers

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This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.

A 58-year-old man with type 2 diabetes mellitus has an asymptomatic plantar ulcer on the left foot that remains unhealed after four months. The ulcer measures 2 cm by 1 cm and is surrounded by callus under the first metatarsal head (Fig. 1). Neurologic examination reveals loss of sensation of light touch, pinprick, and vibration below the midcalf level bilaterally and the absence of ankle reflexes; the foot pulses are normal. How should this patient be evaluated and treated?

THE CLINICAL PROBLEM

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Foot ulcers develop in approximately 15 percent of patients with diabetes, and foot disorders are a leading cause of hospitalization among such patients.¹⁻³ Eighty-five percent of lower-limb amputations in patients with diabetes are preceded by foot ulceration,² suggesting that prevention and appropriate management of foot lesions are of paramount importance. Ulceration is caused by several factors acting together, but particularly by neuropathy.⁴ The annual incidence of foot ulceration is slightly more than 2.0 percent among all patients with diabetes⁵ and between 5.0 and 7.5 percent among diabetic patients with peripheral neuropathy.⁶ Peripheral neuropathy results in loss of the protective sensation of pain and in autonomic dysfunction, with sympathetic denervation, dry skin, and warm feet. Appropriate medical education regarding early assessment for lesions or warning signs of imminent ulceration in patients with sensory loss is essential.

Other important component causes of ulceration include peripheral vascular disease, callus, edema, and deformity. The triad of neuropathy, deformity, and trauma is present in almost two thirds of patients with foot ulcers.⁴ Inappropriate footwear is the most common source of trauma.⁷

The economic burden associated with diabetic foot ulceration — a condition that is preventable in many cases — is enormous. The estimated cost of treating one foot ulcer over a two-year period is \$28,000.⁸ Intensive preventive strategies, including patient education, foot care, and the use of appropriate footwear, may be cost effective or even cost saving if applied to patients with risk factors for foot ulcers.⁹ In a European study, neuropathy accounted for the majority of foot ulcers and had the highest incidence of microvascular complications¹⁰; these complications increased the annual cost of care by 70 percent.

STRATEGIES AND EVIDENCE

DIAGNOSIS

Ulcer Assessment

If the ulcer has been present for months and is asymptomatic and if foot pulses are palpable, neuropathy should be considered as a major cause. However, given the variability

of assessment of foot pulses, noninvasive assessment of the peripheral circulation is recommended if there is any suggestion of peripheral ischemia¹¹ (Fig. 2).

Neuropathy can be detected with a simple neurologic examination of the lower extremities involving the use of a 10-g monofilament, to test sensation, or a composite score such as a modified neuropathy disability score⁵ (Table 1); both are predictive of the risk of foot ulcers. Equipment such as the biothesiometer permits semiquantitative assessment of the vibration-perception threshold, which also predicts the risk of foot ulcers.⁶

Callus formation and a plantar site of ulceration also suggest neuropathy as a major contributory cause. A combination of lack of sensation, limited joint mobility, autonomic dysfunction resulting in dry skin, and repetitive high pressure may lead to callus formation.¹² The relative risk of ulcer development at an area of high pressure (i.e., the metatarsal heads, as compared with the mid-foot) is 4.7, and that of an ulcer developing at a site of callus is 11.0.¹³

Although there is no generally accepted classification system for ulcers, the University of Texas system,¹⁴ which takes into account the size and depth of the ulcer as well as the presence or absence

of infection and ischemia, appears to be a good predictor of the outcome.¹⁵

Infection of the Ulcer

Infection is usually a consequence, rather than a cause, of ulceration, which allows the entry and multiplication of microorganisms.¹⁶ Because all skin wounds harbor microorganisms, swab cultures are not useful in clinically uninfected patients, and infection of diabetic foot ulcers is therefore diagnosed clinically.¹⁷ A commonly accepted definition of foot infection is the presence of systemic signs of infection (e.g., fever, leukocytosis) or purulent secretions, or two or more local symptoms or signs (redness, warmth, induration, pain, or tenderness).^{3,16} Since foot infection has the potential to threaten the limb, appropriate diagnosis and therapy are urgently required. If infection is present, a deep-tissue specimen should be obtained aseptically, if possible; such specimens are superior to superficial swab specimens for the isolation of resistant organisms.¹⁸ Polymicrobial isolates, including aerobic and anaerobic species, are common.^{17,18}

Osteomyelitis

No consensus exists on the optimal criteria for diagnosing osteomyelitis, but up to two thirds of diabetic patients with foot ulcers may have osteomyelitis.¹⁹ The findings on plain radiographs are often suggestive of osteomyelitis (manifested as bone destruction or periosteal reaction, especially as compared with findings on prior films) and radiographs are therefore recommended by many experts when there is evidence of infection. Histologic evaluation and culture of a bone-biopsy specimen are regarded as the gold standard, although differences in outcome that are based on this approach remain to be established.¹⁷ In one study, the ability to probe bone with the use of a blunt, sterile, stainless-steel probe had a positive predictive value of 89 percent for osteomyelitis,²⁰ but this finding requires confirmation. Although white-cell scans are sensitive for the diagnosis, magnetic resonance imaging (MRI) is now considered the imaging test of choice when osteomyelitis is suspected; the sensitivity and specificity of MRI for osteomyelitis in diabetic patients are 90 percent or greater.²¹

MANAGEMENT

The principles of management of neuropathic ulcers include eradication of infection and removal of pressure from the ulcer.



Figure 1. The Neuropathic Ulcer Described in the Vignette, after Adequate Sharp Débridement.

Diabetes and General Care

Direct evidence of a link between glycemic control and healing is lacking; however, glycemic control is likely to be important, since leukocyte function is impaired in patients with chronic hyperglycemia.²² Patients with nephropathy have a risk of amputation that is three times as high as the risk among patients without nephropathy. Although low plasma protein levels may contribute to poor healing,²³ the relative benefits and risks (to the kidney) of increasing protein intake in these patients remain unknown. Patients should be advised to stop smoking, not only because smoking may affect vascular factors, but also because smokers have higher

rates of incisional-wound infections than nonsmokers or former smokers.²⁴

Preparation of the Wound Bed

Preparation of the wound bed is intended to enhance endogenous healing or facilitate the effectiveness of other therapeutic measures.²⁵ Débridement — the removal of necrotic and senescent tissue as well as foreign and infected material from the wound — is a crucial part of this process.²⁶ Although autolytic, enzymatic, or chemical débridement may be used, sharp débridement is common and has been the most thoroughly studied.²⁷ Sharp débridement involves the removal of callus (Fig. 1)

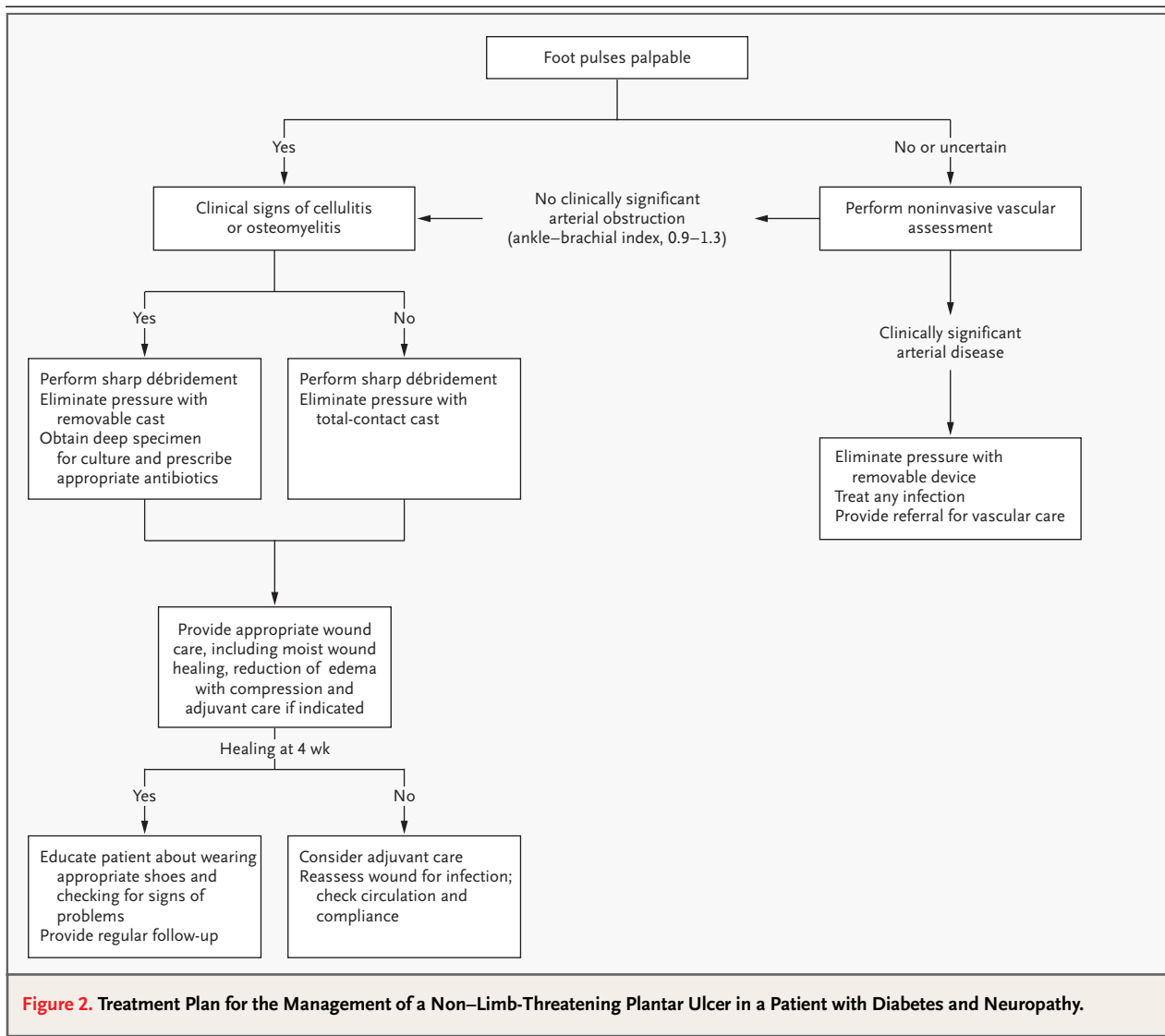


Figure 2. Treatment Plan for the Management of a Non-Limb-Threatening Plantar Ulcer in a Patient with Diabetes and Neuropathy.

Table 1. Neuropathy Disability Score in Patients with Diabetes.*

| Sensation | Score |
|--|-------|
| Vibration threshold (apply 128-Hz tuning fork to apex of great toe) | |
| Normal (can distinguish between presence and absence of vibration) | 0 |
| Abnormal | 1 |
| Temperature (to dorsum of foot, apply a tuning fork placed in a beaker of ice water or warm water) | |
| Normal (can distinguish between hot and cold) | 0 |
| Abnormal | 1 |
| Pinprick (apply pin proximal to great toenail to barely depress skin) | |
| Normal (can distinguish sharpness or lack of sharpness) | 0 |
| Abnormal | 1 |
| Achilles' reflex | |
| Present | 0 |
| Present with reinforcement | 1 |
| Absent | 2 |
| Total for one foot | 0–5 |

* A score (for both feet) of 6 or greater is predictive of foot ulceration. The annual risk of ulceration is 1.1 percent if the score is less than 6 and 6.3 percent if it is greater than or equal to 6.

and may be carried out with the use of a scalpel and forceps. Regular (weekly) sharp débridement has been associated, independently of other therapy, with more rapid healing of ulcers than has less frequent débridement.²⁷

Preparation of the wound bed also includes the treatment of local edema. In a randomized, controlled trial, sharp débridement followed by intermittent foot compression by a pneumatic pump resulted in a higher rate of healing at 12 weeks (75 percent) than did sharp débridement alone (51 percent).²⁸

Removal of Pressure

The benefit of removing pressure from a neuropathic foot ulcer (i.e., reducing mechanical stress, or off-loading) is well established.³ Techniques for removing pressure include the use of casts or boots, halfshoes, sandals, and felted foam dressings. Use of a total-contact cast (i.e., a nonremovable cast) over the involved limb has been shown to be superior to standard therapy and other techniques for removing pressure.^{29,30} In one study, the use of a total-contact cast was associated with more rapid healing of ulcers at every visit over a 12-week peri-

od than was the use of a removable walking cast or half shoe³⁰ (mean healing time, 33.5, 50.4, and 61.1 days, respectively). Increased adherence to treatment may explain the superiority of a total-contact cast over other devices,³¹ since patients are unable to remove the total-contact cast and since they take fewer steps when using it. Patients take more steps in their own homes, where they are less likely than elsewhere to wear a removable prescribed shoe or orthotic device.^{30,31} In one of the studies noted above, patients for whom a removable walking cast had been prescribed for the treatment of plantar ulcers wore the device for only 28 percent of all footsteps, despite having been advised to wear it continuously.³¹

Histologic examination of ulcer specimens has shown that patients treated with total-contact casts before débridement have better healing (indicated by angiogenesis with the formation of granulation tissue) than patients treated with débridement alone (indicated by a predominance of inflammatory elements).³² This finding suggests that, with the use of off-loading, the prevention of repetitive trauma associated with walking improves healing.

Expertise is required to apply a total-contact cast correctly, and applying and removing such a cast, which often must be done weekly, take time. As an alternative, making a walking cast unremovable — for example, by wrapping it in plaster (a so-called instant total-contact cast) — though less well studied, may be beneficial.³³ Contraindications to total-contact casts and other unremovable casts include infected or ischemic wounds, assessed as indicated above.³

Dressings

The development of dressings that promote a moist environment to assist healing has been a focus of care for chronic wounds.³⁴ The selection of a dressing involves matching the properties of the dressing (such as control of exudates) with the characteristics of the ulcer and the patient. Normal-saline moist-to-dry dressings are the most commonly used in the United States; however, they do not provide a sufficiently moist environment and may cause nonselective tissue destruction. Newer dressings include those containing a cellulose-modulating or collagen-protease-modulating framework (Promogran, Johnson and Johnson) and those containing the matrix replacement agent hyaluronan (Hyalofill, ConvaTec).³⁴ These dressings have

not been assessed in large, well-designed trials.³⁵ In one randomized trial comparing Promogran with moistened gauze, there was no difference in outcome.³⁶ However, the means of removing pressure was not standardized among centers, which may explain, in part, the lack of a benefit.

Treatment of Infection

There are few data from randomized trials to help guide antibiotic therapy,¹⁶ and recommended strategies are based largely on clinical experience.¹⁷ There is no compelling evidence that antibiotics should be prescribed for a patient who has a foot ulcer without clinical signs of infection.³⁷ However, clinically infected foot ulcers require treatment guided by appropriate cultures. Although the optimal duration of antibiotic treatment is unknown, continuous use of antibiotics until the ulcer has healed is not recommended. Soft-tissue infections usually require one to two weeks of therapy, whereas osteomyelitis may require more than six weeks of antibiotics, often accompanied by surgical débridement of infected bone.¹⁶

The choice of antibiotic for infected foot ulcers is initially based on the pathogens presumed to be present. Commonly used broad-spectrum antibiotics include clindamycin, cephalexin, ciprofloxacin, and amoxicillin-clavulanic acid (Augmentin).¹⁶ Intravenous antibiotic options for more serious infections (e.g., cellulitis) include imipenem-cilastatin, β -lactam- β -lactamase inhibitors (ampicillin-sulbactam and piperacillin-tazobactam), and broad-spectrum cephalosporins. A newer antibiotic, linezolid, which is active against gram-positive cocci, including many resistant strains, was shown in a randomized trial to be as effective as aminopenicillin- β -lactamase inhibitors in the treatment of foot infections in patients with diabetes.³⁸ Detailed algorithms for the management of foot infections are available.¹⁷

ADJUNCTIVE TREATMENTS

Given the suboptimal healing rates often observed in practice (which may be attributed, in part, to inadequate reduction of pressure), adjunctive treatments have been proposed.

Growth Factors

Recombinant platelet-derived growth factor (becaplermin [Regranex, Ortho-McNeill]) was the first

growth factor approved by the Food and Drug Administration (FDA) for the treatment of neuropathic foot ulcers in patients with diabetes. The most successful of four placebo-controlled trials of platelet-derived growth factor resulted in a moderate improvement in the rate of healing at 20 weeks (50 percent in the group treated with platelet-derived growth factor vs. 35 percent in the placebo group).³⁹ A recent review of growth factors in the treatment of diabetic foot ulcers concluded that, although other growth factors did not appear to improve healing, platelet-derived growth factor may be useful in chronic, nonhealing neuropathic ulcers that do not respond to conventional care.⁴⁰

Tissue-Engineered Skin

Tissue-engineered skin (Apligraf, Organogenesis) comprises a cultured living dermis and sequentially cultured epidermis, the cellular components of which are derived from neonatal foreskin.⁴¹ In a randomized trial involving 208 patients, the rate of healing at 12 weeks was higher among those who used tissue-engineered skin (applied weekly for up to 5 weeks) and received good wound care (débridement and elimination of pressure) than among those who received good wound care alone (56 percent vs. 38 percent, $P=0.004$). Treatment with tissue-engineered skin was associated with faster healing and lower rates of osteomyelitis (3 percent, vs. 10 percent in the control group; $P=0.04$) and lower-limb amputation (6 percent vs. 16 percent, $P=0.03$).⁴² Dermis derived from human fibroblast (Dermagraft, Smith and Nephew) is an allogeneic living-dermis equivalent. In a trial that led to approval by the FDA, 30 percent of wounds treated with fibroblast-derived dermis healed after 12 weeks, as compared with 18 percent of wounds in the control group.⁴³ The low rate of healing reported in the control group suggests that the patients in this group either had particularly refractory ulcers or, more likely, did not comply with pressure reduction.

The failure to reduce the size of an ulcer after four weeks of treatment that includes appropriate débridement and pressure reduction should prompt consideration of adjuvant therapy. It is not yet known whether patients with a high risk of a poor outcome (due to the size and duration of the ulcer) might benefit from earlier application of these therapies. Current adjunctive therapies are limited by their substantial costs.

 DELIVERY OF CARE

Several clinicians and specialties may be involved in the care of patients with foot ulcers, and close collaboration among primary care and specialty care providers is needed. Referral for specialty care should be considered for more complicated or unresponsive lesions. Such integration of services between primary and secondary care has been shown to improve outcomes.⁴⁴

Patients with diabetes, and particularly those with neuropathy, have an increased risk of depression. Since poor foot care is more likely in persons who are depressed than in those who are not, patients at increased risk for ulcers should be screened for depression.⁴⁵

 AREAS OF UNCERTAINTY

PREVENTION

Whereas regular podiatric care is indicated for patients with diabetes who have risk factors for foot ulcers (neuropathy, prior ulceration, vascular disease, or foot deformities),^{12,13} the efficacy of several proposed approaches to prevention remains unproven.⁴⁶ A systematic review of randomized, controlled trials of screening and education of high-risk patients reported conflicting results.⁴⁷ Optimal approaches to education are uncertain, but at a minimum, patients at risk for foot ulcers should understand the implications of sensory loss (i.e., loss of protective sensation) and learn to check for and recognize impending foot problems.

Inappropriate footwear often contributes to neuropathic foot ulceration,⁷ and appropriate footwear with adequate depth and width is recommended to protect the feet. There are conflicting data regarding the benefit of specialized footwear in patients with a history of ulcer; one study suggested that there was a benefit,⁴⁸ whereas another study questioned the efficacy of therapeutic shoes.⁴⁹ In view of the recognized link between inappropriate footwear and ulcer development,⁷ the conflicting data regarding specific footwear should not result in a lack of attention to footwear in high-risk subjects.

THERAPY

Although a recent study showed the efficacy of the instant total-contact cast,⁵⁰ more research on different approaches to pressure reduction is warranted. Further studies of the efficacy of growth factors and

other adjunctive therapies are also required. Other approaches, such as electrical stimulation, the administration of hyperbaric oxygen, and hydrotherapy, are used as adjuvant therapies, but supporting data are lacking. A small randomized trial in which intermittent negative pressure was applied to a wound to stimulate cellular proliferation (Vacuum Assisted Closure, Kinetic Concepts) showed moderate improvement in the rate at which ulcers healed, and larger trials are planned.⁵¹

 GUIDELINES

The American Diabetes Association publishes annual clinical-practice recommendations on preventive foot care⁵² (at www.diabetes.org/for-health-professionals-and-scientists/cpr.jsp). A clinical-practice guideline was presented by the American College of Foot and Ankle Surgeons in 2000.⁵³ The International Working Group on the Diabetic Foot published practical guidelines in 1999.⁵⁴ These guidelines (at www.diabetic-foot-consensus.com) are supported in part by data from clinical trials and in part by expert opinion and are in general agreement with the principles of management outlined above.

 CONCLUSIONS
AND RECOMMENDATIONS

All patients with diabetes should have a thorough foot examination at least annually; those with risk factors (neuropathy, a history of ulcers, vascular disease, or foot deformities) require more frequent monitoring. Patients with sensory loss require regular podiatric care and should be educated regarding preventive foot care. We recommend shoes with adequate depth and width.

Noninfected neuropathic foot ulcers, such as the one described in the vignette, require débridement and reduction of pressure. Although the frequency of visits to the clinic depends on the severity of the ulcer and the response to therapy, weekly visits are reasonable initially for wound débridement and assessment. We recommend the use of a total-contact cast to ensure compliance with pressure reduction, although alternative approaches may be used. Ulcers with signs of clinical infection should be treated with sharp débridement, and deep wound or tissue specimens should be cultured, with antibiotic therapy directed at the isolated pathogenic

organisms. For ulcers that do not respond to standard care, the addition of platelet-derived growth factor and tissue-engineered skin may result in a moderate improvement in healing, but the costs of

these treatments are currently high. A flow chart for the management of plantar ulcers is presented in Figure 2.

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