New therapeutic options for lower-extremity ulcers

Adequate debridement, control of infection, off-loading of pressure, and appropriate topical management are the most important interventions in treating nonhealing wounds. New treatments such as recombinant human growth factors and skin substitutes can help expedite healing.

LEON R. BRILL, DPM, FACFAS, CWS
President, North Texas Podiatric Medicine and Surgery Associates; and attending surgeon, Limb Salvage Center, Dallas, Tex.

JEFFREY A. STONE, DO, MPH, CWS
Medical Director, Hyperbaric Unit, Institute for Exercise and Environmental Medicine, Presbyterian Hospital of Dallas, Dallas, Tex

Article at a glance

Wound management

- Neuropathic ulcers can often be debrided aggressively and promptly without anesthesia because of the patient's inability to feel pain. For hyperesthetic patients, use a local anesthetic without epinephrine. Topical lidocaine gel can also help reduce or eliminate pain associated with debridement.
- Infection with methicillin-resistant *Staphylococcus aureus* (MRSA) and enterococci is a common complication. Vancomycin-resistant organisms, particularly staphylococci and enterococci, are becoming an alarming problem.
- Off-loading pressure on the injured limb is as important as debridement and infection control.
- Becaplermin is the only growth factor to receive FDA approval for lower-extremity diabetic neuropathic ulcers.
- Bioengineered dermal substitutes when implanted into a clean, well-debrided diabetic ulcer help in restoring the injured dermal bed and ultimate re-epithelization.
- Negative pressure wound therapy (VAC) has moved to the forefront in the treatment of complex diabetic foot ulcers.
- Hyperbaric oxygen therapy may stimulate angiogenesis, although the precise mechanism has yet to be elucidated

The incidence of diabetes has increased to epidemic proportions. Over the next 2 decades the incidence of diabetes will go up by 60% in the United States. One fifth of patients with diabetes will develop foot ulcers at some point in their lifetime. Improper or incomplete care of the feet in people with diabetes can increase the prevalence of nonhealing lower-extremity ulcers that may, in turn, lead to serious sequelae. Diabetic foot ulcers are the most common cause of lower-extremity amputations. The majority of these ulcers are a cumulative result of reduced sensation in the feet from neuropathy, acute or repetitive trauma, and reduced blood flow to the feet from peripheral vascular disease (PVD) (see Figure 1, page 00). An American Diabetes Association consensus group found that among persons with diabetes, the risk of foot ulceration was increased among men, patients who had diabetes for more than 10 years, and those with poor glucose control or with cardiovascular, retinal, or renal complications.1 Because 30% of ulcers recur, patients must be educated regarding foot hygiene and reevaluated at regular intervals.

WOUND MANAGEMENT TECHNIQUES

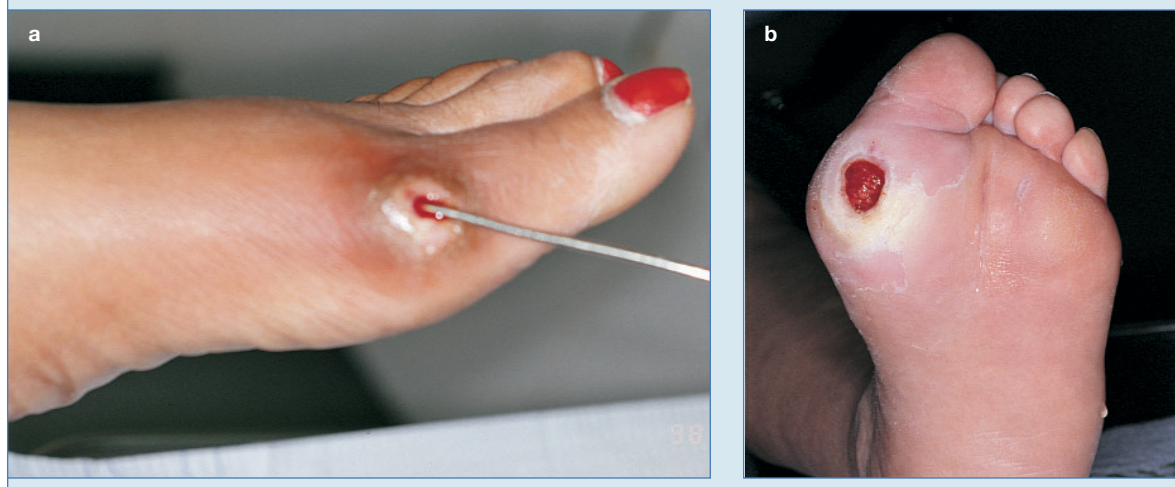
In performing a thorough assessment of ulcers, determine the following characteristics:

- Etiology
- Location
- Size
- Depth or stage of development
- Presence of exudate
- Occurrence of necrotic tissue
- Signs of infection
- Wound oxygenation.

The University of Texas Health Science Center Diabetic Wound Classification System is commonly used for classifying foot ulcers. It is helpful for evaluating wound depth, infection, and PVD in every category of wound assessment (see Table 1, page 00).

Adequate debridement, control of infection, off-loading of pressure, and appropriate topical management are the most important therapeutic interventions in treating nonhealing wounds.and new treatments, such as recombinant human

FIGURE 1



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The dorsal portion of the toes (a) and the plantar aspect of the metatarsophalangeal joints (b) are the usual locations of foot ulcers in patients with diabetes.

growth factors and skin substitutes, can help expedite healing.

Adequate debridement

To properly heal, ulcers must be clean and free of infection and necrotic tissue. Wound healing is impaired when any of the following is present: eschar, purulence, infection, or large areas of necrotic tissue. If wound healing is to occur, areas of devitalized or compromised tissue must first be removed by aggressive debridement, preferably by sharp surgical debridement. Neuropathic ulcers can often be debrided aggressively and promptly without anesthesia because of the patient's inability to feel pain.

In patients with primarily ischemic lesions, marginal neuropathic sensation may render them hyperesthetic. In this case, the best course of pain management is to use a local anesthetic without epinephrine. The use of topical lidocaine gel can also help reduce or eliminate pain associated with surgical debridement.

Callus and necrotic tissue must be completely excised to provide a clean ulcer base for granulation tissue formation and reepithelialization. The clinical importance of adequate debridement is widely recognized. Study results showed that high rates of debridement enhanced the ulcer healing rate of patients treated with the topical recombinant growth factor becaplermin more than the already increased rate of healing provided by it alone.[2] Several methods of debridement can be used with diabetic foot ulcers.

Surgical Considered the gold standard, this method completely removes hyperkeratotic tissue, excess fibrin, and necrotic tissue. Because it causes minimal destruction of tissue and only a mild to moderate amount of bleeding, sharp surgical debridement can be easily performed in an office setting. Instruments needed include a number 10 or number 15 scalpel, small dissecting scissors, forceps, and a medium-sized bone curette.

Mechanical Some clinicians use high-pressure water sprays such as pulsed lavage to wash away excess debris. Even a 30-cc syringe with an 18-gauge needle can provide enough pressure to perform mechanical debridement. The use of whirl-

Drugs mentioned in this article

Amoxicillin/clavulanate (Augmentin)
Becaplermin (Regranex)
Ciprofloxacin (Cipro)
Clindamycin (Cleocin)
Daptomycin (Cubicin)
Imipenem/cilastatin (Primaxin)
Levofloxacin (Levaquin)
Lidocaine gel
Linezolid (Zyvox)
Piperacillin/tazobactam (Zosyn)

TABLE 1
Diabetic wound classification system of the University of Texas Health Science Center, San Antonio

	Grade			
	0	**I**	**II**	**III**
A Nonischemic clean wounds	Preulcerative or postulcerative lesion completely epithelialized	Superficial wound, not involving tendon, capsule, or bone	Wound penetrating to tendon or capsule	Wound penetrating to bone or joint
B Infected nonischemic wounds	Preulcerative or postulcerative lesion, completely epithelialized with infection	Superficial wound, not involving tendon, capsule, or bone with infection	Wound penetrating to tendon or capsule with infection	Wound penetrating to bone or joint with infection
C Ischemic wounds	Preulcerative or postulcerative lesion, completely epithelialized with ischemia	Superficial wound, not involving tendon, capsule, or bone with ischemia	Wound penetrating to tendon or capsule with ischemia	Wound penetrating to bone or joint with ischemia
D Infected ischemic wounds	Preulcerative or postulcerative lesion, completely epithelialized with infection and ischemia	Superficial wound, not involving tendon, capsule, or bone with infection and ischemia	Wound penetrating to tendon or capsule with infection and ischemia	Wound penetrating to bone or joint with infection and ischemia

Adapted with permission from Lavery LA, Armstrong DG, Harkless LB. Classification of diabetic foot wounds. *J Foot Ankle Surg.* 1996;35:528-531.

pools is controversial because of the possibility of burning or macerating the skin.

Autolytic Moisture-retentive dressings, such as films and hydrocolloids, may induce autolytic debridement by allowing enzymes in the body's serum to lyse tissue under the dressing. Leukocytes that collect under the dressing in the wound die and release lysosomal enzymes that degrade proteins and mucopolysaccharides. These moisture-retentive dressings should not be used in infected wounds.

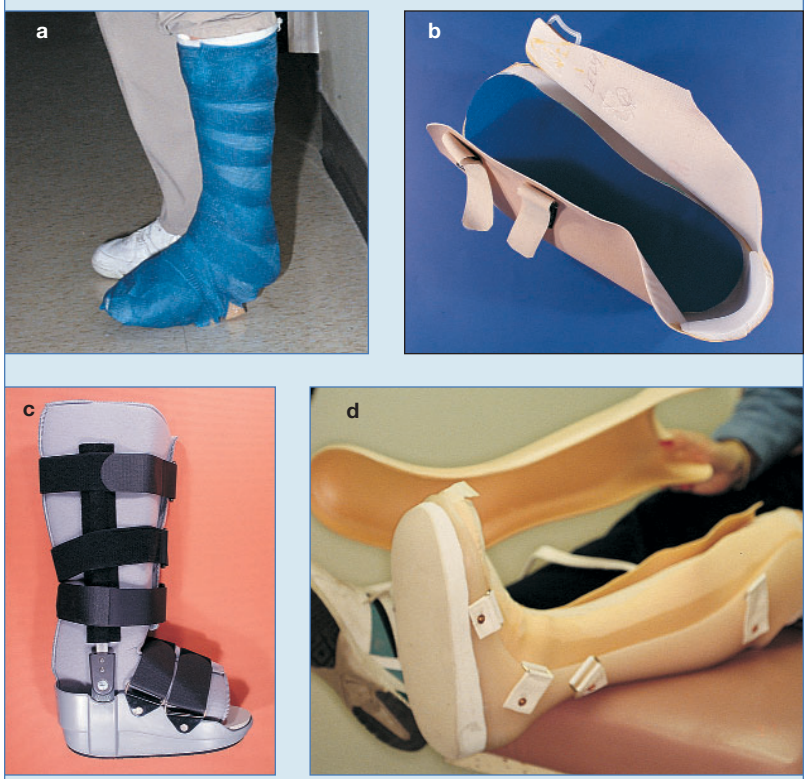
Infection control

An increased risk of infection exists with lower-extremity diabetic ulcers. Infections interfere with the wound healing process and may result in local abscesses, septicemia, and osteomyelitis. The repair process is impeded if the inflammatory response is prolonged or excessive because of the presence of chronic, low-grade infection. Bacterial levels greater than 10^5 colonies per g of tissue can hamper wound healing. If necrotic tissue is also present, sharp debridement may help decrease the bacterial cell count to less than 10^5 colonies per gram of tissue.

Antimicrobial therapy is indicated for infected lower-extremity diabetic ulcers when cellulitis, septicemia, or osteomyelitis is present. Specific therapy should be guided by culture results of soft tissue aspirates, blood cultures, or bone biopsy. The route of administration should be decided based on severity and extent of the wound, GI absorption, and a patient's tolerance.

Infection with methicillin-resistant *Staphylococcus aureus* (MRSA) and enterococci is a common complication of lower-extremity diabetic ulcers. As with infections in general, vancomycin-resistant organisms, particularly staphylococci and enterococci, are becoming an alarming problem. This is most likely a result of chronic use of antibiotics and antiseptics in an immunocompromised host. MSRA- and vancomycin-resistant -infected wounds may require combined antimicrobial therapy, at least in the initial treatment

FIGURE 2



A total contact cast (a), a total contact sandal (b), or a short leg walker (c) can be used to off-load pressure on an injured limb. A clamshell brace (d) is cut to create an anterior and posterior shell, allowing easy access to wound care.

IMAGES: LEON R. BRILL, DPM

stages. Two new antibiotics available for use in MRSA and vancomycin-resistant enterococci (VRE) infections are linezolid, an oxazolidinone, which is available in both oral and parenteral forms, 600 mg every 12 hours, and daptomycin, a new class of lipopeptide, given as 4 mg/kg IV every 24 hours. Note that tissue, rather than swab cultures, should be obtained prior to instituting antibiotic therapy, when possible, because of the excessive use of antimicrobial agents

For mild to moderate infections, some physicians prescribe a penicillinase-resistant penicillin, such as amoxicillin/clavulanate, 875 mg/125 mg bid for 10 to 14 days. If the patient has an allergy to penicillin, give a quinolone antibiotic such as ciprofloxacin, 500 mg bid, or levofloxacin, 500 mg/d. When prescribing an antibiotic, keep in mind that the majority of diabetic foot ulcers tend to be polymicrobial, although 75% to 80% have MRSA and enterococci as a primary pathogen. For more serious infections, the patient can be started with piperacillin/tazobactam, 3.375 g IV q6h. If an anaerobic infection is suspected, add clindamycin, 150 to 300 mg/d either IV or po in divided doses q6h. A good alternative until definitive culture and sensitivities are reported is imipenem/cilastatin, 500 mg/500 mg IV q6h.

Topical disinfectants, such as povidone iodine, acetic acid, hydrogen peroxide, and sodium hypochlorite, may be cytotoxic to fibroblasts and may actually impair wound healing. Studies have found that the cellular toxicity of these disinfectants outweighs their antimicrobial benefits.

Off-loading pressure

Off-loading pressure on the injured limb is as important as debridement and infection control. Without adequate off-loading, any progress that has been made in the treatment of the wounded foot will be halted or even reversed.

Available devices to off-load wounds range from wheelchairs, crutches, and walkers, to total contact casts, total contact sandals, short leg walkers, and wedged healing shoes. Therapeutic footwear, such as running shoes, extra depth shoes, and custom molded shoes should be reserved for a foot that has healed.). Various materials, such as pealite, Plastizote, and ethylene vunyl acetate (EVA) may be used alone or in combination and molded to the patient's foot to cushion and off-load high pressure areas. Total contact casts are useful for off-loading pressure on the forefoot, but less useful for off-loading the heel (see Figure 2, page 00). Casting requires specialized techniques and is best achieved through the use of a podiatrist or pedorthist. Any movement

of the foot within the cast may produce new wounds. Variations of the total contact cast for wound access include bivalving and clamshell braces that have been cut to create an anterior and posterior shell. These allow not only for effective off-loading but also for easy access to wound care. Although all these devices are effective in off-loading the wounded foot, there are no adequately controlled studies to demonstrate superiority of one variety over the other.

FIGURE 3

The dressing for negative pressure wound therapy is attached by tubing that provides subatmospheric or negative pressure that can be applied continuously or intermittently.

IMAGE:

Topical use of recombinant growth factors

The discovery of growth factors in the 1970s and 1980s, as well as the development of recombinant DNA technology for the production of growth factors in large quantities, revitalized the area of wound healing. To date, becaplermin is the only growth factor to receive FDA approval for the treatment of lower-extremity diabetic neuropathic ulcers. An average ulcer wound would require a 15-g tube at a cost of $400 to $500. Currently, Medicare does not cover becaplermin, and third-party payers vary in their reimbursement policies.

In a pivotal, multicenter study of patients with full-thickness, nonhealing lower-extremity diabetic ulcers, subjects were assigned randomly to receive topical treatment with either becaplermin, formulated in a water-based, carboxymethylcellulose sodium gel, or a placebo gel until complete wound closure was achieved or for a maximum of 20 weeks. Compared with placebo gel, becaplermin gel, 100 mcg/g, significantly increased the incidence of complete healing by 43% and decreased the time to achieve complete wound healing by 32%.[3]

Skin substitutes

Bioengineered tissues developed through the use of recombinant DNA technology in the last 2 decades have contributed to better and quicker wound healing outcomes. The 2 most widely used are Apligraf and Dermagraft, both of which are in the category of living skin equivalents or dermal substitutes. These bioengineered dermal substitutes contain many of the same components of human dermis, including various growth factors, cytokines, matrix proteins, and glycosaminoglycans to name a few. When implanted into a clean, well-debrided diabetic ulcer, they help in restoring the injured dermal bed and ultimate reepithelization. The major differences between the 2 products: Apligraf is a bilayered product containing keratinocytes grown on a bovine platform and Dermagraft is a single-layered product containing no keratinocytes, which is grown on a bio-absorbable platform of polyglactin mesh. Both products are indicated for diabetic foot ulcers of at least 6 weeks duration that have not responded to good, conventional wound care.

Negative pressure wound therapy

Within the last several years, negative pressure wound therapy (VAC) has moved to the forefront in the treatment of complex diabetic foot ulcers. VAC is composed of an open foam cell dressing that is conformed into the wound and then sealed by an outer airtight adhesive dressing (see Figure 3, page 00). The dressing is attached by tubing to a pump that provides subatmospheric pressure (negative) that can be applied continuously or intermittently. Although it is not well-understood, the probable mechanism of healing

TABLE 2
Progression of dressings for infected ischemic wounds

Wound healing phase	Description	Dressings	Rationale
Inflammatory (or reaction) phase	Infected, yellow sloughy wound	Calcium alginate rope	Absorb wound exudate; promote autolytic debridement
Granulation	Red, granulating wound	Hydrocolloid paste and dressing	Fill wound cavity (dead space); provide moisture-retentive, occlusive microenvironment
Reepithelialization (or remodeling) phase	Pink, resurfacing wound	Hydrocolloid dressing only	Protect epithelial buds and new epithelium

Adapted with permission from Krasner D, Kane D (eds). *Chronic Wound Care: A Clinical Sourcebook for Healthcare Professionals.* 2nd ed. Wayne, Pa; Health Management Publications, Inc. 1997:140-144.

involves providing a moist wound healing environment and exudate management as well as a decrease in bacterial load, an increase in wound temperature, and cellular stimulation, all of which have been shown to provide maximum wound healing potential.

Hyperbaric oxygen therapy

Administration of high concentrations of oxygen at greater than atmospheric pressure (hyperbaric oxygen therapy) increases the amount of dissolved oxygen carried in the bloodstream by approximately 30%.[5]

Hyperbaric oxygen therapy enhances wound healing by increasing local delivery of oxygen to ischemic tissues. Studies suggest that hyperbaric oxygen therapy may stimulate angiogenesis, although the precise mechanism has yet to be elucidated. One study that measured transcutaneous oxygen tension in healing tissue in the diabetic foot demonstrated an improvement in capillary blood flow during 3 weeks of hyperbaric oxygen therapy, as evidenced by increasing tissue oxygen tension. Similar changes were observed in ischemic irradiated tissue.

Protocols for the use of hyperbaric oxygen vary on the basis of severity. In the absence of infection, once-daily treatment with hyperbaric oxygen at 2.0 to 2.4 atmospheres absolute for 90 to 120 minutes is sufficient for stimulation of wound healing. Although treatment sessions are brief, subcutaneous tissue oxygen tension may remain elevated for many hours after exposure.[6]

Recent evidenced-based technology reviews have found hyperbaric oxygen therapy to be of benefit in treating certain diabetic wounds that fail conservative therapy.[7-9] The Centers for Medicare and Medicaid Services will cover hyperbaric oxygen therapy only in the setting of a hospital, either inpatient or outpatient diabetic wounds of the lower extremities in patients who meet the following 3 criteria:

- Patient has type I or type II diabetes and has a lower extremity wound that is due to diabetes
- Patient has a wound classified as Wagner grade III or higher
- Patient has failed an adequate course of standard wound therapy.

Appropriate wound dressings

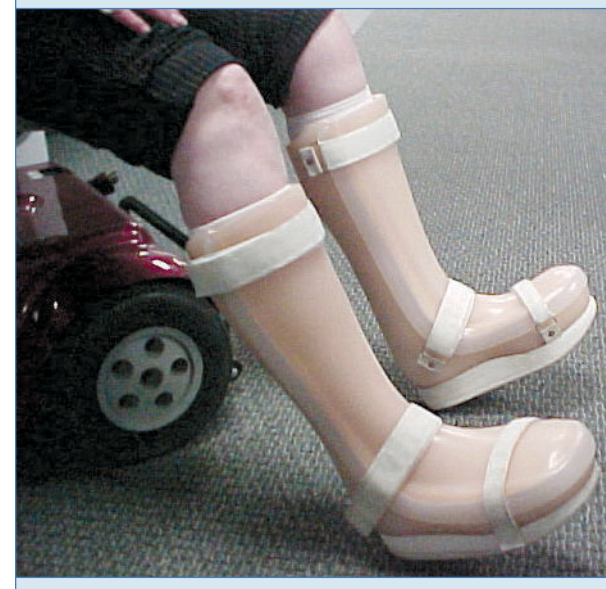
Dressings for wounds may be designed to allow moisture to escape or may be occlusive. Saline gauze dressings involve placement of a saline-dampened gauze onto the ulcer bed. Before the gauze is removed, it is rewetted with saline to facilitate removal and to avoid damage to healthy tissue. Advantages of using this type of dressing are that it is inexpensive, easy for patients or caregivers to apply, and may aid in wound debridement by facilitating the removal of residual bits of necrotic tissue. A disadvantage is that such dressings may require frequent changes.

Occlusive dressings, commonly made of adhesive hydrocolloid or polyurethane film, retain moisture and increase reepithelialization (see Table 2, page 00).[10] They do this by preventing

eschars and crusts that tend to form in a dry wound environment and impede the migration of epidermal cells. Other advantages of occlusive dressings are that they may decrease pain, reduce wound contamination, and facilitate autolytic debridement.

Because hydrocolloid dressings promote an acidic environment around the wound, increased enzymatic activity may be expected. Although these dressings have been shown to promote healing of certain types of chronic wounds, increased activity of enzymes may result in degradation of newly produced tissue, and dressing material may incorporate into the wound bed, hindering epithelial migration.[11] Another disadvantage is that they can only be used on infection-free wounds. Thus, they require careful patient monitoring, since the moist environment they provide is conducive to bacterial growth.

FIGURE 4



The Charcot's foot restraint orthotic walker covers the entire foot and calf, providing support by preventing foot and ankle movement.

IMAGE:

Charcot's foot

Neuropathic osteoarthropathy, otherwise known as Charcot's foot, is a particularly debilitating condition that leads to gross deformity and dramatically increases the risk for ulceration and amputation. Although the etiology is poorly understood, it is thought that major or minor trauma in the presence of autonomic dysfunction and strain on tissues that have already undergone tissue glycosylation set in motion a chain of events, including arteriovenous shunting, rapid washout of calcium from bone, rupture of ligaments, primarily but not only in the mid foot, which leads to fracture, dislocation, and ultimately deformity of the foot.

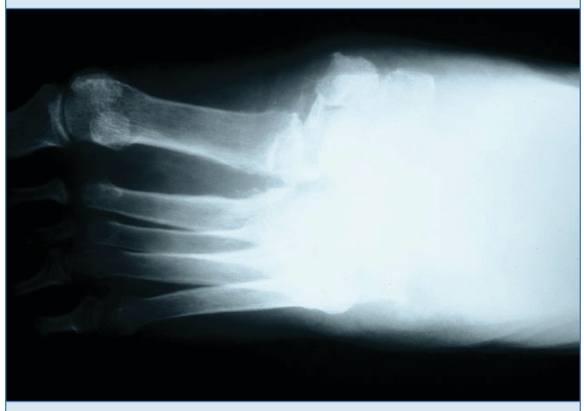
The incidence of Charcot's foot ranges from between 0.16% in the general diabetic population to 15% in a neuropathic foot population. The most important pearl in treatment is recognition. Onset may be subtle or rapid. Neuropathic osteoarthropathy initially manifests as a warm, swollen, and erythematous foot but early signs of this condition are commonly mistaken for cellulitis. The initial treatment is off-loading and immobilization in a total contact cast, short-leg walker, or complete nonweightbearing with crutches or wheelchair. There are some small anecdotal studies that indicate the adjunctive use of bisphosphonates and calcium may be helpful in slowing down bone destruction and increasing bone regeneration and consolidation. Specialized shoe wear and possible bracing are a must in follow-up (see Figure 4, page 00). In advanced deformity, reconstructive surgery to maintain a functional limb should be considered.

FOLLOW-UP CARE

Regular follow-up examinations of patients with lower-extremity diabetic ulcers are an important component of treatment. Exams should be performed weekly until the ulcers have healed enough to warrant biweekly treatments. Once the foot ulcers have sufficiently healed, patients (and their shoes) should be checked at least every 2 months until stable and then every 6 months. Even patients whose ulcers have healed must be reevaluated at regular intervals, since approximately 30% of ulcers recur.[4]

Lower-extremity diabetic ulcers are best managed with a multidisciplinary team effort that includes nursing, medical, surgical, and rehabilitative services, as well as the patient and family

FIGURE 5



Plain radiography can be used to confirm the structural abnormalities of Charcot's foot.

IMAGE:

members. Communication among health care professionals and between health care professionals and the patient is essential.

Testing for neuropathy

Each patient with diabetes should be routinely tested for neuropathy. The simplest and least expensive test for sensory neuropathy is Semmes-Weinstein aesthesiometry. In this test a nylon monofilament with a premeasured thickness is placed against the patient's foot in multiple locations to test for sensation of pressure. In patients with neuropathy, the monofilament cannot be felt. This tool allows for the early diagnosis of loss of sensation due to peripheral neuropathy. If neuropathy is suspected, the diagnosis should be confirmed with thermal discrimination tests (detection of hot and cold) and biothesiometry (vibratory sensation with a tuning fork).

Signs of wasting, weakness, or absent tendon reflexes indicate motor neuropathy, whereas reduced sweating, changes in skin texture, existence of callus, and distended dorsal foot veins suggest autonomic neuropathy. These findings may be confirmed with electrophysiologic tests (motor neuropathy) or a quantitative sweat test and noninvasive Doppler testing (autonomic neuropathy) if necessary. Assessing foot pulses and noting skin temperature and pallor may provide an indication of vascular status of the affected limb, although more tests may be necessary to fully assess vascularity. Toe deformities, hallux valgus, prominent metatarsal heads, or Charcot's foot often contribute to abnormal stress patterns in the foot. It may be necessary to confirm structural abnormalities with radiography (see Figure 5, page 00).

Patient education

Patient education is the most important factor in preventing the initial development of lower-extremity ulcers and recurrence of ulcers that have healed. It may also reduce the risk of amputation.[4,12,13] Patient care should be directed toward nutritional repletion, improvements in tissue oxygenation, and, in pressure-sensitive areas, perfusion. Mobility and ambulation should be encouraged when feasible. High-calorie protein and carbohydrate-rich diets are beneficial.

There will be no magic bullet in the treatment of diabetic foot ulcers, but rather new and improved combinations of technologies and therapies that target the underlying pathophysiologic mechanism. New and combined growth factors, cytokine enhancers and inhibitors, and gene therapy will hopefully improve outcomes and reduce the incidence of lower-extremity amputations in the future. □

PRODUCED BY DEBORAH KAPLAN

Dr Brill discloses that he serves on an advisor board for Johnson & Johnson and on a speaker's bureau for Cubis Pharmaceuticals.

Dr Stone discloses that he serves on speakers' bureaus for Smith & Nephew and Johnson & Johnson.

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