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# Protocol for treatment of diabetic foot ulcers

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**Abstract**

Each year, 82,000 limb amputations are performed in patients with diabetes mellitus. The majority of these amputations could be avoided by following strict protocols. The collective experience treating patients with neuropathic diabetic foot ulcers of 4 major diabetic foot programs in the United States and Europe were analyzed. The following protocol has been developed for patients with diabetic foot ulcers: (1) measurement of the wound by planimetry; (2) optimal glucose control; (3) surgical debridement of all hyperkeratotic, infected, and nonviable tissue; (4) systemic antibiotics for deep infection, drainage, and cellulitis; (5) offloading; (6) moist-wound environment; and (7) treatment with growth factors and/or cellular therapy if the wound is not healing after 2 weeks with this protocol and a new epithelial layer is not forming. In addition, the pathogenesis of diabetic foot ulcers is discussed, as well as the associated costs and complications, including amputation. Debridement, wound-bed preparation, antibiotics, various types of dressings, biological therapies, growth factors, and offloading are described as treatment modalities for patients with diabetic foot ulcers. In diabetic foot ulcers, availability of the above modalities, in combination with early recognition and comprehensive treatment, ensure rapid healing and minimize morbidity, mortality, and costs, as well as eliminate amputation in the absence of ischemia and osteomyelitis. © 2004 Excerpta Medica, Inc. All rights reserved.

Every year, 82,000 limb amputations are performed in patients with diabetes mellitus. The majority of these amputations are performed in the elderly population [1]. Amputations resulting from diabetes may arise from multiple etiologies, including foot ulcers, ischemia, venous leg ulcers (ie, those secondary to venous reflux), and heel ulcers (ie, those resulting from untreated pressure ulcers in the heel). The majority of these amputations originate from ulcers [2]. The prevalence of foot ulcers among patients with diabetes is 12% [3]. In addition, the 20-year cumulative incidence of lower-extremity ulcers in patients with type 1 diabetes is 9.9% [4, 5]. This article focuses on all types of diabetic foot ulcers. Venous disease is not addressed. Diabetes-induced limb amputations result in a 5-year mortality rate of 39% to 68% and are associated with an increased risk of additional amputations [6]. The length of hospital stay is approximately 60% longer among patients with diabetic foot ulcers, as compared with those without ulcers [6].

After a patient with diabetes develops an open wound, closure of the foot wound is hampered by both physiologic impairments in wound healing and an increased susceptibility to wound infection. Guidelines for prevention and treatment of diabetic foot ulcers [7–11] emphasize that healing is accelerated and that morbidities and amputations are decreased if infection is prevented and adequate offloading is achieved.

We present herein an evidence-based protocol that has proved highly effective in our clinical practices (Fig. 1). Strict adherence to this protocol ensures that almost every patient's ulcer will heal. However, evidence-based protocols are not available currently for treatment of wounds complicated by osteomyelitis and ischemia. Patients with these conditions often heal after a series of orthopedic or vascular reconstructions and should be treated by an experienced foot team. Healing rates for diabetic foot wounds complicated by osteomyelitis and ischemia cannot be precisely predicted because these protocols have not been established through rigorous clinical trials.

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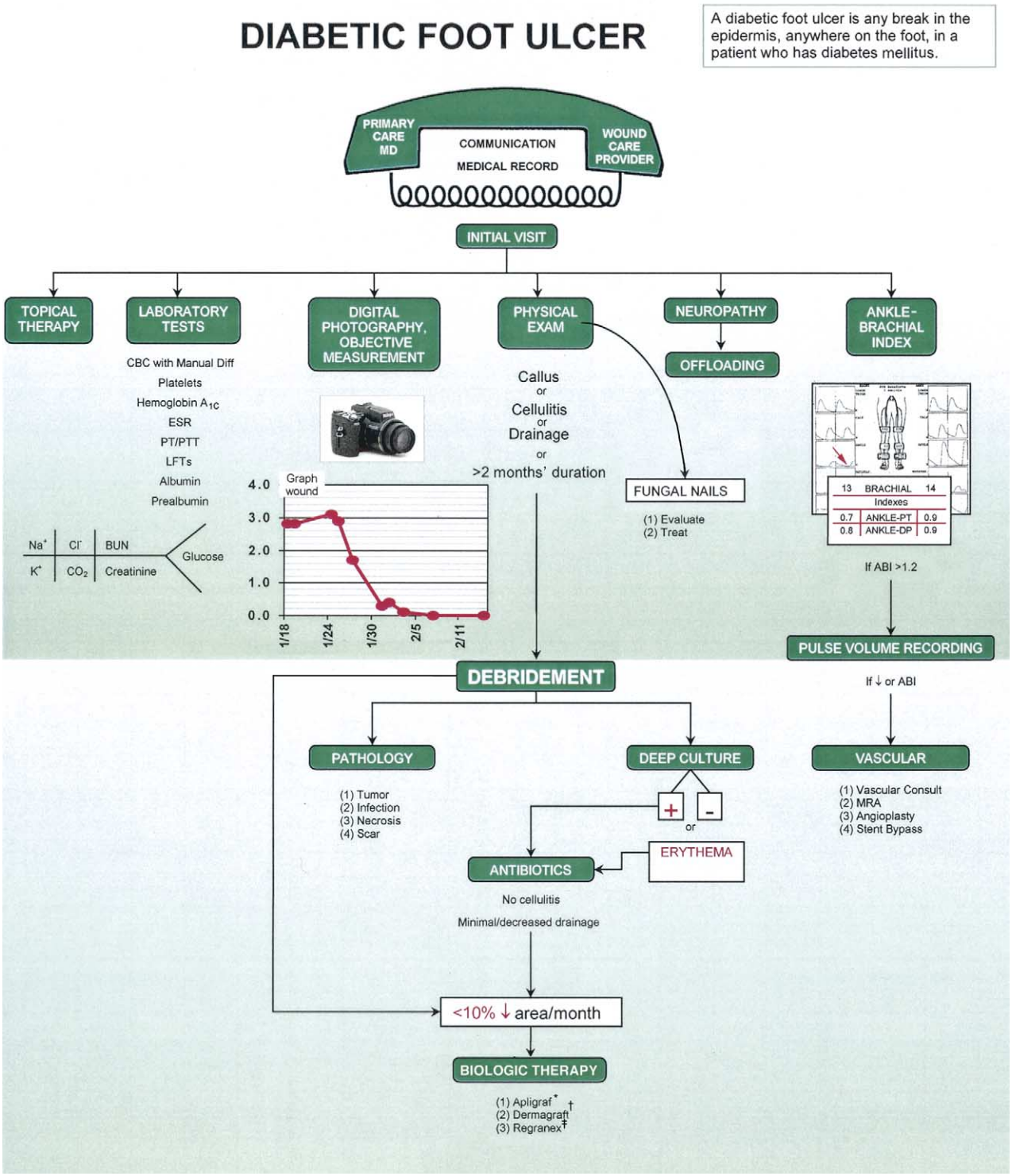


Fig. 1. Diabetic foot ulcer. ABI = ankle-brachial index; ANKLE-DP = dorsalis pedis; ANKLE-PT posterior tibia; CBC = complete blood count; Diff = differential; ESR = erythrocyte sedimentation rate; LFTs = liver function tests; MRA = magnetic resonance angiography; PT = prothrombin time; PTT = partial thromboplastin time. * Human skin equivalent; Organogenesis, East Hanover, NJ. † Nicryl mesh; Smith & Nephew, London, United Kingdom. ‡ Becaplermin; Ortho-McNeil, Raritan, NJ.

## Amputation

Amputation remains a major source of morbidity, and occasionally mortality, among patients with diabetes because of the high incidence of foot ulcers [6,12]. Diabetes accounts for >60% of all nontraumatic lower-leg amputations [13]. The risk of lower-limb amputation is 30 to 40 times higher in the diabetic, as opposed to the nondiabetic, population [14]. Surgical revision of initial amputations, and multiple amputations to contralateral or ipsilateral

limbs, are also common in patients who receive foot amputations [15].

Studies in some underdeveloped countries indicate that patients with severe diabetic foot ulcers who do not undergo surgery have a mortality rate of up 54% within 2 years [16].

## Costs

The expenses associated with diabetic foot ulcers that remain unhealed are substantial, both for the patient and the health care system [6]. In 2002 alone, it is estimated that the costs associated with diabetes in the United States were $132 billion; $92 billion of this total was related to direct medical expenditures for these patients; the remaining $40 billion was related to lost productivity [17]. Diabetes results in higher rates of lost work time, disability, and premature mortality.

During a 2-year period, the medical costs for a single patient with diabetes between 40 and 65 years of age with a foot ulcer has been estimated at approximately $28,000 [18]. This figure reflects only direct medical costs and does not include the costs associated with continued care or amputation. Costs for amputation range from $20,000 to $60,000 annually per patient [19]. Even these estimates do not take into account how these ulcers affect the personal, social, and economic aspects of a patient's life.

## Pathogenesis

### *Neuropathy*

Nerve damage in diabetes affects the motor, sensory, and autonomic fibers. Motor neuropathy causes muscle weakness, atrophy, and paresis. Sensory neuropathy leads to loss of the protective sensations of pain, pressure, and heat. The absence of pain leads to many problems in the insensate foot, including ulceration, unperceived trauma, and Charcot neuroarthropathy. The patient may not seek treatment until after the wound has advanced. A combination of sensory and motor dysfunction can cause the patient to place abnormal stresses on the foot, resulting in trauma, which may lead to infection. Autonomic sympathetic neuropathy causes vasodilation and decreased sweating, which results in warm, overly dry feet that are particularly prone to skin breakdown, as well as functional alterations in microvascular flow [20]. Autonomic dysfunction (and denervation of dermal structures) also results in loss of skin integrity, which provides an ideal site for microbial invasion [7]. The neuropathic foot does not ulcerate spontaneously; rather, it is the combination of some form of trauma accompanied by neuropathy. The most common causal pathway to diabetic foot ulceration can thus be identified as the combination of neuropathy (sensory loss), deformity (eg, prominent metatarsal heads), and trauma (eg, ill-fitting footwear) [21].

Diabetes and pressure can impair microvascular circulation and lead to changes in the skin on the lower extremities, which in turn, can lead to formation of ulcers and subsequent infection. Diabetic neuropathy impairs the nerve axon reflex that depends on healthy C-fiber nociceptor function and causes local vasodilation in response to a painful stimulus. This condition further compromises the vasodilatory response present in conditions of stress, such as injury or inflammation, in the diabetic neuropathic foot. This impairment may partially explain why some ulcers in the diabetic neuropathic foot are either slow to heal or fail to heal at all, despite successful lower-extremity revascularization [22].

### *Ischemia*

Ischemia can be divided into 2 categories: the first involves the accelerated atherosclerosis that occurs commonly in patients with diabetes, ie, in the femoral, popliteal, and posterior tibial arteries. These vessels, often only 1 or 2 cm in diameter, can develop atherosclerotic plaque, which seriously decreases blood flow. After large vessels become completely occluded, stroke, myocardial infarction, ischemia, and nonhealing diabetic foot ulcers can occur. This form of ischemia is essentially a large-vessel disease.

Decreased angiogenesis in a diabetic wound is the other form of ischemia. Although promising therapies (eg, vascular endothelial growth factor) have been effective in treating cardiac disease and neuropathies, they are not currently available for treatment of diabetic foot ulcers; however, they are in clinical trial.

Most surgeons prefer to perform popliteal or tibial arterial bypass because of inferior rates of limb salvage and patency compared with more proximal procedures. If popliteal or tibial arterial bypass is unable to restore a palpable foot pulse, pedal bypass has been reported to provide a more durable and effective limb-salvage procedure for patients with diabetes and ischemic foot wounds [23]. Even extensive multisegment occlusive disease in patients with diabetes does not present an impediment to foot salvage. Whereas serious wound complications may have disastrous results, they are uncommon after pedal bypass grafting. Adequate control of preexisting foot infection and careful graft tunneling have been shown to be effective in avoiding further complications. Angioplasty in the lower extremity is becoming more progressively utilized. However, it must be emphasized that for angioplasty to be effective, a distal vessel or feeding vessel must be patent if the more proximal angioplasty is to succeed.

## Initial evaluation

Diabetic foot ulcers are chronic wounds that do not heal unless treated actively and, in the case of plantar ulcers, offloaded; in neuropathic ulcers it is often what is taken off the wound that is most important (eg, callus, pressure).

Chronic foot wounds fail to heal in an orderly manner and result in a consequent compromise of anatomic and functional integrity because of an underlying physiologic impairment (eg, decreased angiogenic response, neuropathy, and ischemia) [24]. Because patients with diabetes exhibit impaired wound healing in addition to increased susceptibility to wound infection, any disruption in the integument is a chronic wound, with its related complications (eg, bacterial colonization of the wound bed, soft tissues, bone, and/or bloodstream). Therefore, early intervention is crucial to successful treatment of these diabetic foot ulcers, and in averting the morbidities and mortality associated with them. Successful intervention requires a thorough understanding of diabetic foot ulcer pathogenesis and rapid implementation of standardized, effective therapy.

Wound healing is a multistep process and in diabetic foot ulcers requires angiogenesis, deposition of extracellular matrix, contraction, and epithelialization [25]. An ideally healed wound has normal anatomic structure, function, and appearance. An acceptably healed wound is characterized by restoration of sustained functional and anatomic continuity [26].

When a patient with a diabetic foot ulcer is first seen, a comprehensive history and treatment plan must be put into place. Additional information to be acquired includes identification of the patient's primary medical physician, and measurement of glycosylated hemoglobin to determine whether glucose levels are controlled adequately on a long-term basis.

Callus formation, especially with hemorrhage, is a sign of impending ulceration. Removal of the callus results in lowered plantar pressures [9]. Therefore, all patients should be examined for callus formation, and serious consideration should be given to whether excision is required.

*Fungal toenails*

Patients with diabetic foot ulcers must be examined carefully for the presence of thickened fungal toenails. Onychomycosis, a fungal infection of the nails, affects approximately 34% of patients with diabetes [27]. Management of patients with onychomycosis and diabetes is complicated by a number of diabetes-related medical factors that contribute to impaired wound healing. These factors may result in a higher risk of onychomycosis-related morbidities in patients with, than in those without, diabetes [28]. For example, some bacterial infections are initiated after injury to the skin by the sharp and brittle nails characteristic of onychomycosis. Furthermore, these infections may go unnoticed by the patient because of the presence of sensory neuropathy [29].

Treatment options for fungal toes include oral antifungal agents (ie, griseofulvin, itraconazole, ketoconazole, terbinafine, fluconazole), topical therapy (ie, ciclopirox nail lacquer 8%, terbinafine), and mechanical intervention [30]. Topical therapy is often preferred over systemic treatment because there is less potential for serious adverse events and significant drug interactions [31]. However, topical therapy is often less effective. Mechanical intervention involves procedures that range from regular grooming of the nails to total surgical nail avulsion. Debridement of infected nails is a useful part of therapy, because it allows reduction of sharp, thick nails and removal of columns of refractory dystrophic nail plates [32]. Onychomycosis is a source of extensive morbidity among patients with diabetes, which severely affects their quality of life. Examination of the toes is a crucial part of the treatment protocol.

*Assessment of arterial blood supply*

The pulses of a patient with diabetes are important to assess, and a normal ankle-brachial index (ABI) in those without diabetes is 0.9 to 1.1. A vascular surgery consultation should be obtained immediately after the first visit if the pulse volume recording has decreased or if the ABI is $<0.9$. All patients with foot ulcers should undergo noninvasive vascular testing. In most vascular laboratories, the ABI is measured by calculating a ratio of pressure at the ankle to pressure in the arm [33].

Noninvasive laboratory tests frequently underestimate the severity of arterial disease in patients with diabetes, who commonly have a falsely elevated ABI. Arterial calcification often occurs in diabetes. When arterial pressures are measured by Doppler echography with use of a blood pressure cuff, a portion of the cuff inflation is used to overcome the rigidity of the vessel wall, which results in a falsely elevated value. Therefore, a different assessment of blood flow should be used. Toe pressures reflect blood flow more accurately in patients with diabetes. Waveforms measured by Doppler echography or pulse volume recording are also helpful. A normal ABI with a markedly dampened waveform suggests calcified vessels and a falsely elevated ABI [33].

If a patient has arterial insufficiency, revascularization (bypass) surgery may be necessary [34]. In patients with diabetes, the pattern of occlusive peripheral arterial disease involves medium-sized arteries, primarily at the popliteal trifurcation. The distal pedal vessels are spared from occlusive disease in patients with diabetes, also called "small vessel disease." Distal arterial bypass grafting surgery to the pedal arteries is practiced commonly in patients with diabetes [23].

Severe arterial occlusion is common among patients with diabetes. Magnetic resonance angiography (MRA) images demonstrate flowing blood and are used successfully for anatomic evaluation of most arterial regions. MRA is able to image blood flow at velocities as slow as 2 cm/sec, and has been proved more accurate than digital subtraction angiography in diagnosing arterial disease [35]. MRA has been shown to be significantly better at disclosing peripheral runoff vessels in patients with diabetes than is digital subtraction angiography [36]. Additional studies have reported

that foot vessels that are not visualized on conventional angiography could be detected by MRA and are shown to be suitable target vessels for pedal bypass grafting [35].

*Special considerations for patients*

Patients should perform self-examinations for indications of breaks in the skin, and if any are found, patients should be examined immediately by a physician. Additionally, patients must be advised to obtain appropriate footwear that adequately protects the foot and sufficiently alleviates pressure. Patients with foot ulcers should refrain from smoking, because smoking reduces the rate of oxygen intake and delivery to the wound site, and retards proper wound repair. Furthermore, nicotine, carbon monoxide, and hydrogen cyanide in smoke have a toxic effect on platelets and inhibit normal cellular metabolism, which creates a deleterious environment for healing [37].

Accurate assessment of the physiologic impairments to healing in a chronic wound is essential when designing a successful treatment plan. The necessity for vascular intervention (eg, bypass or stent) must be assessed in all patients with extremity ulcers and impairment in arterial inflow. All patients with diabetes and those at risk for localized pressure (ie, spinal cord–injured and bed-bound patients) should have all of their skin examined daily. A new break in the skin in these patients requires immediate intervention.

## Osteomyelitis

Osteomyelitis is present in many diabetic foot ulcers [38] and is treated most effectively by surgical removal of the infected bone. After the infected bone is removed, the patient requires only antibiotics for control of bacteria in the surrounding soft tissue. Demineralization, periosteal reaction, and bony destruction—the classic radiographic triad of osteomyelitis—appear only after 30% to 50% of bone destruction, a process that takes up to 2 weeks [39]. In addition, soft-tissue infection is difficult to differentiate from bone infection in patients with diabetes and neuropathic disease. However, accurate diagnosis is crucial, and antibiotic treatments vary greatly in time, cost, and effectiveness, depending on the presence or absence of osteomyelitis [40].

Several imaging techniques aid in determination of osteomyelitis in patients with diabetes. These include image-guided bone biopsy [40], magnetic resonance imaging (MRI) [39–43], 3-phase bone scans [40,44,45], leukocyte scans [39–41,44,46,47], and computed tomography (CT) [39,47,48]. The results of imaging tests are presented in terms of sensitivity and specificity: sensitivity reflects ability of the test to identify all cases in which osteomyelitis is present, whereas specificity indicates ability of the test to identify only cases without osteomyelitis. Accuracy is the ability to determine correctly whether osteomyelitis is present [41]. With the availability of these diagnostic tools, early diagnosis is necessary for successful treatment. We recommend routine baseline bilateral x-rays on all patients first seen with a diabetic foot ulcer. All nonhealing wounds should be monitored by an MRI.

## Management

*Debridement*

Debridement is the first and most important step in healing a diabetic ulcer [4]. The foundation of comprehensive care for diabetic foot ulcers is removal of all nonviable, infected tissue (including bone) from open wounds, as well as surrounding calluses, until a new border of healthy, bleeding soft tissue and uninfected bone is created. More extensive ulcers should be debrided in the operating room.

Surgical debridement with a sharp knife (even if down to the bone) can remove all devitalized portions of a wound so that scar and infection are no longer present and has proved safe and therapeutic. The wound margins should be extended approximately 2 to 3 mm into healthy, bleeding, soft nonhyperkeratotic skin.

Debridement is necessary before application of other wound-closure procedures and improves the outcome of diabetic foot ulcers independent of topical and growth factor treatments [49]. Sharp excisional debridement accomplishes 4 goals: it (1) removes local contaminated bacteria; (2) stimulates healing; (3) documents the absence of hyperkeratotic tissue and tumor; and (4) decreases local infection. The importance of adequate debridement and prevention of morbidities in the patient with diabetic foot ulcers is exemplified in Figure 2.

*Infection*

Diabetic foot ulcers act as portals of entry for systemic infection (from cellulitis, infected foot ulcers, and osteomyelitis), which can have particularly deleterious effects on patients with diabetes, whose impaired immunity increases their risk for local and systemic infection [50,51]. A bacterial culture of the deepest portion of the wound should be obtained when a patient is first seen with a diabetic foot ulcer if there is clinical evidence of infection. Infections in patients with diabetic foot ulcers are commonly polymicrobial and contain both aerobic and anaerobic bacteria [37]. Deep infections require early surgical debridement of all devitalized tissue, followed by antibiotic treatment to address the polymicrobial nature of the infection [7]. Although topical antibiotics may be useful to treat superficial infections, studies have shown that traditional topical antibiotic creams and ointments alone are not effective universally in chronic or acute wounds, nor are they specifically successful in uncomplicated diabetic neuropathic forefoot ulcers [52].

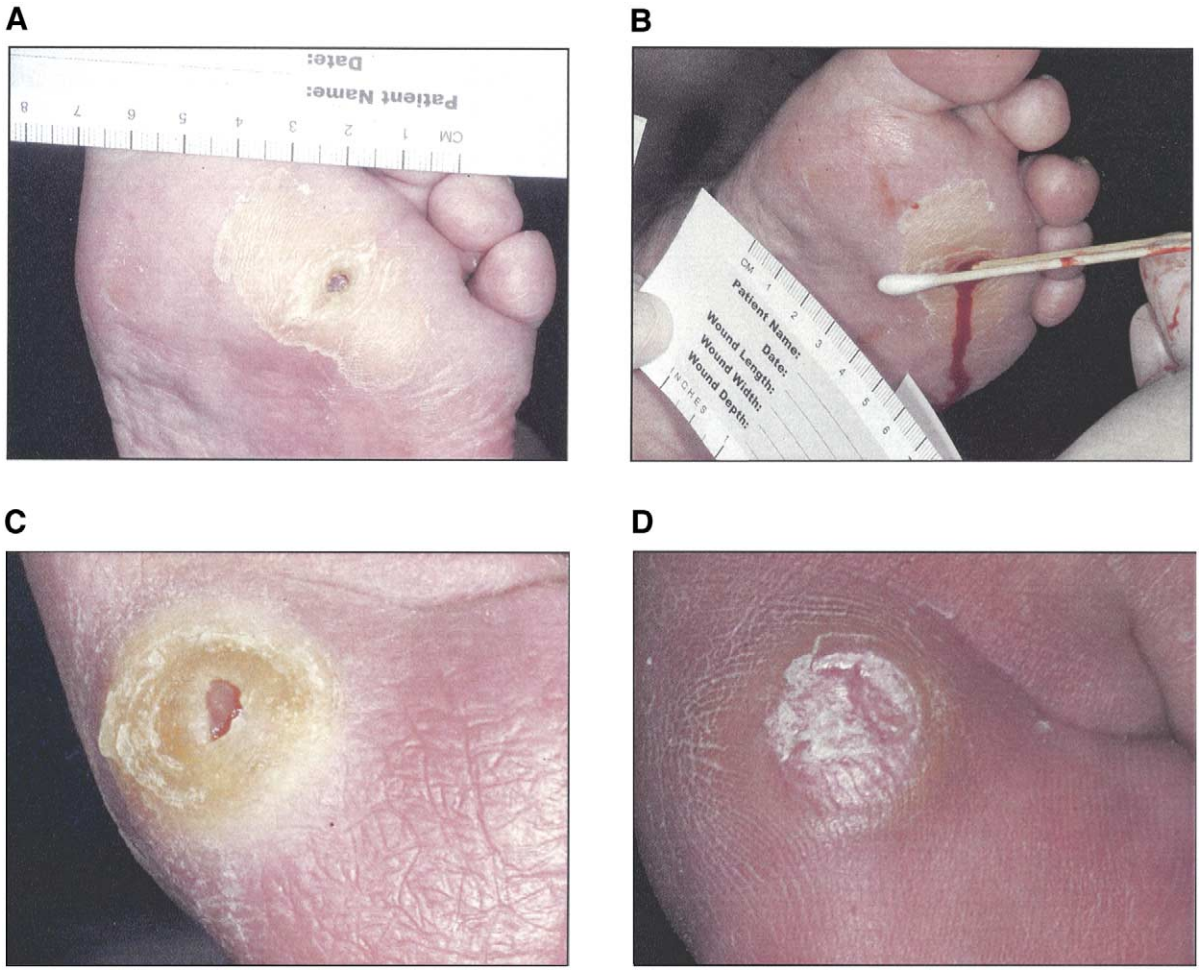


Fig. 2. (*A*) This ulcer was not debrided for months. A callous, and open ulcer is an absolute indication for debridement in a diabetic patient with a plantar foot ulcer. (*B*) There was a significant amount of undermining, despite the appearance that the wound was not a serious ulcer. This patient subsequently presented with an infected foot ulcer and significant morbidity. (*C*) In contrast, the ulcer of this patient with diabetes was immediately debrided. (*D*) The ulcer rapidly healed.

Topical antiseptics, such as hydrogen peroxide, povidone, iodine, and acetic acid, are toxic to healing dermal cells and should be avoided [7].

Parenteral antibiotics should be used to treat serious infections or to achieve higher concentrations of antibiotics in the peripheral tissues. Oral antibiotics and outpatient management may not be successful in treating infected diabetic foot wounds because of poor vascularization. When oral antibiotics and outpatient management are attempted, the wound-care clinician must make daily assessments of the wound to ensure it is not worsening and change management immediately if a worsening wound is observed.

Local bacterial contamination is always present in a nondebrided wound, and because of diabetic immune system impairments, sepsis is possible. Debridement and antibiotic therapy must be initiated as early as possible. Hyperglycemia also should be monitored closely and controlled, because it may increase the virulence of microorganisms.

## Offloading

It has been established that minor traumas, such as repetitive stress and shoe pressure, are significant components of the etiology in the pathway to ulcerations [8,21]. Peak plantar pressures are highest in the forefoot, compared with the rear foot and medial arch [53]. Reducing pressure applied to the wound, especially in the forefoot, is essential for optimal treatment. Concurrently, irregular biomechanics, such as those caused by limited joint mobility and/or structural foot deformity, can contribute to abnormal pressure on the plantar foot surface. Even light pressure applied to a healing wound can be detrimental to healing [37]. Unrelieved pressure impairs healing and increases the risk of complications. The most studied and effective offloading technique for treatment of neuropathic wounds, especially those midmost, is total contact casting (TCC) [33], considered the “gold standard” for offloading [53]. A TCC is

minimally padded and molded carefully to the shape of the foot. These special casts redistribute weight off the ulcer site and allow patients to walk while the ulcer heals. Although this method is extremely successful for treating diabetic foot ulcers, not all diabetic foot ulcers are candidates for TCC. Frequent wound inspection and daily dressing changes are not possible, which renders these casts unsuitable for ischemic ulcers [37]. TCC also requires experienced technicians trained specifically in this application. When applied inappropriately, there is a risk of the ulcer worsening and an infection being missed. Because of the drawbacks of TCC, many new offloading modalities are being investigated. Two examples are removable cast walkers and half-shoes [53]. A promising new technique takes a removable cast walker and renders it irremovable by wrapping it with cast material [54]. If ongoing trials show its efficacy to be equivalent to TCC, then its use will become more widespread.

The goal of tissue-load management is to create an environment that enhances soft-tissue viability and promotes wound healing. In addition to the vigilant use of proper-positioning techniques, support surfaces designed to decrease the magnitude of pressure, friction, and shear, while providing appropriate levels of moisture and temperature that support tissue health and growth, should also be used.

*Objective wound measurement*

Only recently have healing rates for diabetic foot ulcers been established that provide a template against which to gauge the effectiveness of any particular treatment. At least once a week, the length and width of the wound must be measured in all patients. Planimetry is optimal, but if not available, a simple ruler may be used. All findings must be documented in the medical record. The ambiguous but commonly heard phrase that a wound "looks good" is not an adequate objective wound assessment and should not be used.

*Wound-bed preparation and dressings*

The goal of wound-bed preparation is to have well-vascularized granulation tissue without signs of local infection (drainage, cellulitis, and odor) [55]. Removing scar tissue is also essential [56]. Proper debridement simultaneously prepares the wound bed and stimulates the healing process. Optimal wound-bed preparation includes stimulation of granulation tissue (new collagen and angiogenesis) and reduction of bacterial burden in the wound. In preparing the wound bed, one must ensure that there is (1) creation of a moist wound-healing environment and facilitation of the formation of granulation tissue, and (2) treatment of the underlying pathophysiology. After debridement of an infected wound, topical antibiotics may be efficacious. The silver cation has been shown to be effective at killing antibiotic-resistant strains of bacteria. Different types of topical long-acting silver applications [57] that are effective include Acticoat (Smith & Nephew plc, London, United Kingdom), Aquacel Ag (ConvaTec, Deeside, United Kingdom), and Actisorb Silver 220 (Johnson & Johnson, New Brunswick, NJ). Cadexomer iodine also uses sustained release of the antimicrobial agent, which results in removal of both the bacterial burden and exudates [58].

After debridement, tissues should be kept moist to prevent formation of devitalized tissue and subsequent deepening of the wound. Keeping a wound moist facilitates more rapid migration of epidermal cells across the wound bed, which enhances epidermal migration and promotes angiogenesis and connective tissue synthesis. Choosing an appropriate local wound dressing requires identification of neuropathic, neuroischemic, and ischemic causes of diabetic foot ulcers. Similarly, treatment of a particular patient varies dramatically depending on the tissue involved; treatment of a superficial skin wound requires a substantially different dressing from treatment of a more extensive wound that involves both skin and bone. A wound actively granulating requires a dressing material different from a wound in the epithelializing phase of healing; a deep sinus wound should be treated differently from a wound that produces copious amounts of exudates [59].

Appropriate dressing types are also determined by wound location, depth, amount of eschar or slough present, amount of exudate, condition of the wound margins, presence of infection, need for adhesiveness, and conformability of the dressing. Dressing selection should be reevaluated periodically to meet these modifications in the wound environment, because the wound changes constantly during treatment [37].

In the past decade, dressing technology has improved significantly, and several new products have been developed for management of various types of chronic ulcers. For example, many dressings today can kill bacteria and facilitate repair. In addition, some of these dressings have been shown to provide a barrier against environmental contamination, bacteria, and some viruses [9].

*Biologic therapies*

All the treatments discussed in the following sections are expensive and should be considered only when patients fail to improve after the approaches described above have been applied for $\geq$2 weeks.

Diabetic foot ulcers exhibit decreases in both angiogenic response and production of growth factors within the wound. Cell therapy, also called biologic therapy, presents an appropriate treatment option in some cases. Accelerating healing time decreases the risk of wound infection. Cultured epidermal autografts can provide permanent coverage of large areas. The US Food and Drug Administration (FDA) approved 2 cell therapies to accelerate the closure of nonhealing ulcers. These 2 commercially available products are fibroblasts in a vicryl mesh, called Dermagraft (Smith &

Nephew), and Apligraf (Organogenesis, East Hanover, NJ), also known as human skin equivalent, which contains both fibroblasts and keratinocytes [60–62].

The fibroblasts of the dermal equivalent proliferate within the scaffold, secreting human dermal collagen, fibronectin, glycosaminoglycans, growth factors, and other proteins, which embed themselves in a self-produced dermal matrix. The result is metabolically active dermal tissue with the structure of papillary dermis of newborn skin [63,64]. This drug may need to be applied weekly.

Human skin equivalent is actually a bilayer, biologically active skin construct, composed of a surface layer of allogeneic human keratinocytes over a layer of allogeneic human fibroblasts, suspended within a collagen matrix [60–62,65]. This treatment has been proved effective in treating ulcers that have been refractory to standard therapy, for example, venous ulcers [55] and pressure ulcers [66]. Fibroblasts synthesize collagen and secrete growth factors essential for wound healing and epithelialization. Keratinocytes secrete substances that stimulate target genes, which control the cellular activation cycle responsible for the wound-healing process.

Human skin equivalent is used following debridement after complete hemostasis is attained. Adaptic (Johnson & Johnson) is then placed over the graft, followed by Vaseline (petroleum jelly; Cheesebrough USA Company, Greenwich, CT) gauze wrapped around sterile cotton, and an occlusive dressing is applied by covering with Tegaderm (3M Health Care, St. Paul, MN). This procedure is performed easily in the outpatient, inpatient, or nursing home setting.

### *Growth factors*

Individual synthetic growth factors can be generated by recombinant DNA technology. Growth factors stimulate cellular proliferation, chemotaxis, angiogenesis, protein expression, and enzyme production, and may act on adjacent cells in a paracrine function, on cells that produce growth factors in an autocrine function, or within the cell in an intercrine function. Growth factors activate cells within the wound to send signals to wound target cells, which initiate tissue repair.

Growth factors applied topically to wounds can accelerate healing by stimulating granulation tissue formation and enhancing epithelialization [67]. Single or isolated growth factors may be effective in healing diabetic ulcers, especially when they influence many different types of cells, such as platelet-derived growth factor (PDGF).

Becaplermin (Regranex; Ortho-McNeil, Raritan, NJ), or recombinant human PDGF-BB (rhPDGF-BB), is a homodimer produced through recombinant DNA technology by inserting the gene for the B chain of PDGF into the yeast *Saccharomyces cerevisiae*. The biologic activity of becaplermin is similar to that of naturally occurring PDGF, and promotes chemotactic recruitment and proliferation of cells involved in the wound-repair process [68].

Becaplermin is formulated in a preserved, sodium carboxymethylcellulose–based gel for topical administration. This aqueous gel provides a moist wound-healing environment with negligible systemic absorption. Becaplermin is well tolerated and represents a pharmacologically active treatment for chronic lower-extremity diabetic ulcers [68]. Becaplermin gel is easy for patients or their caregivers to apply in an informal clinical setting, and it has an excellent safety profile [68–70]. The FDA approved becaplermin gel in December 1997 as a supplement for treatment of lower-extremity diabetic neuropathic ulcers that extend into the subcutaneous tissue or beyond and have an adequate blood supply. PDGF-BB was the first, and to date only, recombinant growth factor to be approved for treatment of a chronic wound [70].

The recommended protocol for administration of Becaplermin is to apply a thin layer to the wound (using a tongue depressor) and then to cover the wound with a saline-moisturized gauze dressing [69].

## Conclusion

All diabetic foot ulcers without ischemia or osteomyelitis should be expected to heal. The status of a wound should not be judged by its appearance. A wound can “look good” but still be a source of infection. Treatment success should be judged by objective measurement of the wound’s healing rate. If all diabetic ulcers are recognized early and treated comprehensively with a regimen that includes proper consideration of the therapies described in these guidelines, then the incidence of osteomyelitis and amputation in nonischemic ulcers will decrease drastically. We propose that all future trials of therapies for plantar neuropathic ulcers should use standardized offloading, preferably with an irremovable device [71], in order to remove the most important confounding variables in previous trials, that is, walking on the ulcer without appropriate pressure relief.

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