Evidence-Based Protocol for Diabetic Foot Ulcers

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Background: Diabetic foot ulcers are the single biggest risk factor for nontraumatic foot amputations in persons with diabetes. Foot ulcers occur in 12 to 25 percent of persons with diabetes and precede 84 percent of all nontraumatic amputations in this growing population. Because of the high incidence of foot ulcers, amputations remain a source of morbidity and mortality in persons with diabetes. Strict adherence to evidence-based protocols as described herein will prevent the majority of these amputations.

Methods: The collective experience of treating patients with neuropathic diabetic foot ulcers in four major diabetic foot programs in the United States and Europe was analyzed.

Results: The following protocol was developed for patients with diabetic foot ulcers: (1) establishment of good communication among the patient, the wound healing team, and the primary medical doctor; (2) comprehensive, protocol-driven care of the entire patient, including hemoglobin A1c, microalbuminuria, and cholesterol as well as early treatment of retinopathy, nephropathy, and cardiac disease; (3) weekly objective measurement of the wound with digital photography, planimetry, and documentation of the wound-healing process using the Wound Electronic Medical Record, if available; (4) objective evaluation of blood flow in the lower extremities (e.g., noninvasive flow studies); (5) débridement of hyperkeratotic, infected, and nonviable tissue; (6) use of systemic antibiotics for deep infection, drainage, and cellulitis; (7) off-loading; (8) maintenance of a moist wound bed; (9) use of growth factor and/or cellular therapy if the wound is not healing after 3 weeks with this protocol; and (10) consideration of the use of vacuum-assisted therapy in complex wounds.

Conclusions: In diabetic foot ulcers, availability of the above modalities, in combination with early recognition and comprehensive treatment, ensures rapid healing, minimizes morbidity and mortality rates, and eliminates toe and limb amputations in the absence of ischemia and osteomyelitis. (*Plast. Reconstr. Surg.* 117 (Suppl.): 193S, 2006.)

By the year 2030, it is estimated that 366 million persons in the world will have diabetes. The worldwide prevalence of diabetes was estimated to be 2.8 percent in 2000 and is expected to grow to 4.4 percent in 2030.[1] The lifetime risk of a person with diabetes developing a foot ulcer could be as high as 25 percent,[2] and it is believed that every 30 seconds a lower limb is lost somewhere in the world as a consequence of diabetes.[3,4] In the United States, 82,000 limb amputations are performed in patients with diabetes mellitus per year, and approximately 54 percent of these amputations are performed in elderly patients aged 65 and older.[5,6] Amputations are 15 times more common in persons with diabetes than in persons without the disease.[7] Diabetes-induced limb amputations are associated with an increased risk of additional amputations and result in a 5-year mortality rate of 39 to 68 percent.[8,9]

Diabetic foot ulcers are the single biggest risk factor for nontraumatic foot amputations in persons with diabetes.[10] Foot ulcers occur in 12 to 25 percent of persons with diabetes[4,5] and precede

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84 percent of all nontraumatic amputations in the growing population of persons with diabetes.[11–13] Due to the high incidence of foot ulcers, amputations remain a source of morbidity and mortality in persons with diabetes.[13,14]

A diabetic foot ulcer is defined as any skin breakdown on the foot of a diabetic person,[15] including even minor irruptions on the toes, heel, and the dorsal and plantar foot. Nonhealing foot ulcers act as portals of entry for systemic infection that can have particularly deleterious effects on patients with diabetes, whose impaired innate immunity significantly increases their risk for infection.[16–18] Furthermore, physiologic impairments as a result of diabetes severely hamper closure of the foot ulcer.[19,20] Guidelines for prevention and treatment of diabetic foot ulcers emphasize that healing is accelerated and morbidities and amputations are decreased if infection is prevented, a moist wound-healing environment is maintained, and adequate offloading is achieved.[4,21–25]

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. Early recognition and treatment can effectively prevent the progression of diabetic foot ulcers to chronic wounds that become recalcitrant to therapy.[26,27] 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.

COSTS

The expenses associated with diabetic foot ulcers that remain unhealed are substantial, both for the patient and the health care system. 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 with diabetes; the remaining $40 billion was related to lost productivity.[28] 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 have been estimated at approximately $28,000.[10,22,29] 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.[30] These estimates do not take into account how these ulcers severely affect the personal, social, and economic aspects of a patient's life.[31]

PATHOGENESIS OF DIABETIC FOOT ULCERS

Neuropathy

Nerve damage in persons with diabetes affects the motor, sensory, and autonomic fibers. Motor neuropathy results in muscle weakness, atrophy, and paresis. Sensory neuropathy leads to loss of the protective sensations to pain, pressure, and temperature. In the absence of pain, many problems in the insensate foot may occur, including ulceration, unperceived trauma, and Charcot's neuroarthropathy. The patient may not seek treatment until after the wound is 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.[13] Autonomic dysfunction (and denervation of dermal structures) also results in loss of skin integrity, which provides an ideal site for microbial invasion.[21] 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 (e.g., prominent metatarsal heads), and trauma (e.g., ill-fitting footwear).[13]

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 explain in part why some ulcers in the diabetic neuropathic foot are either slow to heal or fail to

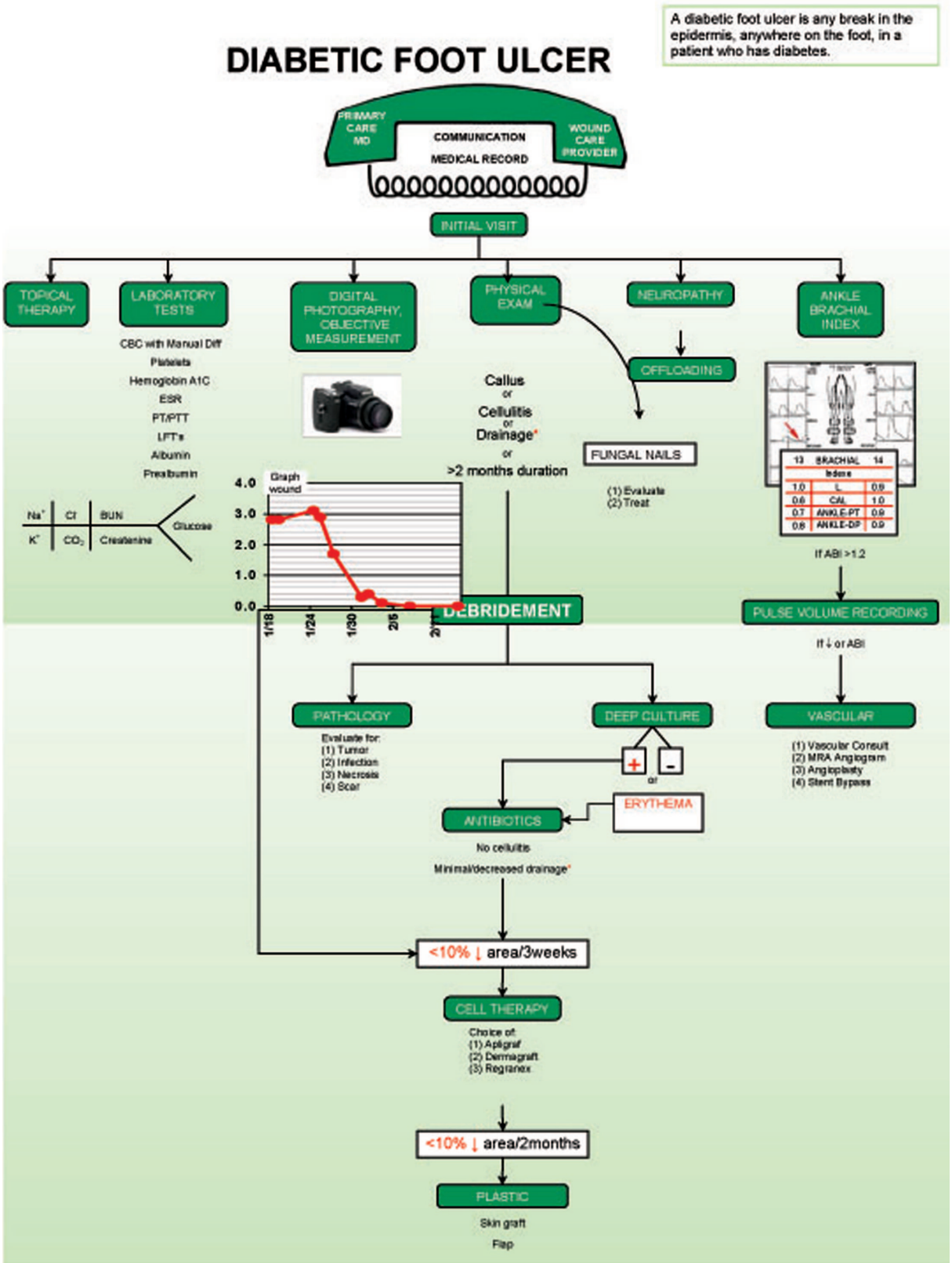

Fig. 1. Protocol for diabetic foot ulcers. *ABI*, ankle-brachial index; *ANKLE-DP*, dorsalis pedis; *ANKLE-PT*, posterior tibia; *CBC*, complete blood count; *Diff*, differential; *ESR*, erythrocyte sedimentation rate; *LFTs*, liver function tests; *MRA*, magnetic resonance angiography; *PT*, prothrombin time; *PTT*, partial thromboplastin time. *Bilayered keratinocytes and fibroblasts (Organogenesis, East Hanover, N.J.). †Nicryl mesh (Smith & Nephew, London, United Kingdom). ‡Becaplermin (Ortho-McNeil, Raritan, N.J.).

heal at all, despite successful lower extremity revascularization.[32]

People with diabetes should have yearly somatosensory testing to evaluate the level of sensation in their feet.[13] One recommended method for determining diabetic peripheral neuropathy is with a 10-g Semmes-Weinstein monofilament.[2,33–35] This examination tests a patient's pressure perception by pressing filament against the skin of the distal plantar foot while the patient's eyes are closed.[36] An alternative method for diagnosing neuropathy is the Pressure-Specified Sensory Device, a useful tool in the identification of the earliest degree of chronic nerve compression and the assessment of a specific nerve.[37,38] A centrally calibrated biothesiometer can be used to measure a patient's threshold of perception of vibration.[14,39] It may be beneficial to refer a patient to a surgeon trained in lower extremity peripheral nerve decompression techniques, which have been shown to restore sensation in more than 80 percent of patients with neuropathy.[40]

Ischemia

Peripheral arterial disease, characterized by arterial stenosis and occlusions, is the product of the advanced atherosclerosis that can occur in patients with diabetes in the femoral, dorsalis pedis, 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 these vessels become completely occluded, stroke, myocardial infarction, limb ischemia, and nonhealing diabetic foot ulcers can occur.[41,42]

Patients with both diabetes and peripheral arterial disease are more prone to ischemic ulceration than those without the disease.[43,44] Although the majority of diabetic foot ulcers are not associated with atherosclerosis of the large vessels in the leg and subsequent ischemia,[44,45] it is perhaps the single most avoidable cause of amputations. We emphasize the need for early revascularization in patients with diabetic foot ulcers. Even if reocclusion were to occur, the advantage of providing temporary revascularization is highly significant, as this may still be sufficient for the wound to heal.

Even extensive multisegment occlusive disease in patients with diabetes does not always present an impediment to foot salvage. Whereas serious wound complications may lead to limb and life loss, they are uncommon after pedal bypass grafting. Adequate control of preexisting foot infection, followed by revascularization, will prevent further complications in the majority of ischemic patients.

Excimer laser-assisted, subintimal angioplasty and percutaneous transluminal balloon angioplasty with or without stents are being used to treat occlusive lesions and stenosis in lower extremity arteries. Endovascular interventions for both claudication and critical limb ischemia have been shown to have high 6- and 12-month patency rates, with limited morbidity.[46–49] Percutaneous transluminal angioplasty proved to be effective in people with diabetes when treating a number of large arteries, including the iliac trunk, profunda femoral, superficial femoral, popliteal, anterior tibial, posterior tibial and peroneal. Patients who underwent angioplasty saw an increase in their ankle-brachial index from 0.53 to 0.90 ($p < .0001$) and an end to ischemic pain following the procedure.[50] These surgical procedures have been suggested as a reasonable alternative for those who cannot accommodate a bypass.[48,51,52] In the presence of limb ischemia, we recommend consideration of angioplasty, and or stenting and or arthrectomy, when it is performed by an experienced clinician working in tandem with the physician supervising the wound healing.

The second category of ischemia involves decreased angiogenesis in the small vessels of the diabetic foot. Although promising therapies (e.g., vascular endothelial growth factor) have been effective in treating cardiac disease and neuropathies, they are not currently available for treatment of diabetic foot ulcers. The need for clinical trails with local angiogenic therapy is clearly evident.

INITIAL EVALUATION

Diabetic foot ulcers are chronic wounds that do not heal unless they are treated actively and, in the case of plantar ulcers, off-loaded; in neuropathic ulcers, it is often what is taken off the wound that is most important (e.g., callus, pressure). Chronic foot wounds fail to heal in an orderly manner and result in a consequent compromise of anatomical and functional integrity because of an underlying physiologic impairment (e.g., decreased angiogenic response, neuropathy, and ischemia).[53] Since 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 (e.g., 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 to 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 it requires angiogenesis, deposition of extracellular matrix, contraction, and epithelialization.[54] An ideally healed wound has a normal anatomical structure, function, and appearance. An acceptably healed wound is characterized by restoration of sustained functional and anatomic continuity.[55] Specifically, a healed wound has no callus and no drainage and is fully epithelialized.

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 blood pressure, height and weight to calculate body mass index, and laboratory values, some of which are known to correlate with complications of diabetes (e.g., heart disease, renal failure, nephropathy, retinopathy, neuropathy, and microalbuminuria).[56–58]

Laboratory Data

The laboratory data collected upon admission should include complete blood count with manual differential, prothrombin time/international normalized ratio/partial thromboplastin time, basic metabolic panel, hemoglobin A1c level, lipid profile, hepatic function panel, prealbumin level, erythrocyte sedimentation rate, thyroid-stimulating hormone level, and urinary microalbumin level. How these factors correlate with foot ulcer healing and amputation rates is a critically important research question.

High glucose concentrations in the blood lead to increased glycation of the hemoglobin molecules to form hemoglobin A1c, which persists in the circulation for up to 6 weeks.[59] Therefore, measurement of plasma hemoglobin A1c is the accepted standard for monitoring long-term glucose control.[59–61] Elevated hemoglobin A1c levels have been correlated with a variety of comorbidities, such as cardiovascular and/or coronary heart disease, retinopathy, neuropathy, and nephropathy/renal failure.[62,63] Hemoglobin A1c should routinely be measured every 4 months.

Low serum high-density lipoprotein, high serum low-density lipoprotein, and high serum triglyceride levels have also been shown to increase cardiac complications in patients with diabetes.[64,65] Hypertension, treated or untreated hypercholesterolemia, hypertriglyceridemia, low high-density lipoprotein cholesterol levels, and obesity (body mass index >30) have been shown to increase risk for heart disease,[66,67] retinopathy,[68] and nephropathy.[69] The lipid profile should be measured monthly if abnormal and every 4 months if normal. Blood pressure should be measured weekly. Height and weight to calculate body mass index should be collected monthly.

There are few options in terms of laboratory tests that indicate the acute nutritional status in persons with diabetes, and there is no accepted standard method for nutritional assessment.[70] The prealbumin level, although not an objective parameter of nutritional status, provides objective data that indirectly correlates with nutritional status. Because of its short half-life of 2 days, prealbumin may be more reliable than albumin in the acute setting. Prealbumin levels have been demonstrated to be significantly lower in patients with nephropathy and in patients with pressure wounds, and malnutrition has been associated with immunodeficiencies that can impair wound healing.[71] In patients with diabetic foot wounds, prealbumin levels should be measured and nutritional status should be optimized.[72–74]

The microalbuminuria test detects small quantities of urine albumin. The main reason this test is performed is for the early detection of diabetic nephropathy. Microalbuminuria has been shown to be a significant risk factor associated with foot ulcers, nephropathy, retinopathy, and cardiovascular disease in patients with diabetes.[75,76] Foot ulcers are more frequent in microalbuminuric and macroalbuminuric patients, at 13 percent and 25 percent, respectively, compared with 5 percent in patients with normal albuminuria, and there is a high prevalence of microalbuminuria (27 percent) and macroalbuminuria (14 percent) in patients with type 2 diabetes.[77] All diabetic patients without known nephropathy should be screened for microalbuminuria annually.

Callus

Callus formation, especially with hemorrhage, is a sign of impending skin breakdown and ulceration. Removal of the callus results in lowered plantar pressures.[23] Therefore, as part the protocol, all patients should be examined for callus formation, and all calluses should be removed, with few exceptions. Débridement should be performed as soon as possible every time a patient develops a callus on his or her foot (Fig. 2).

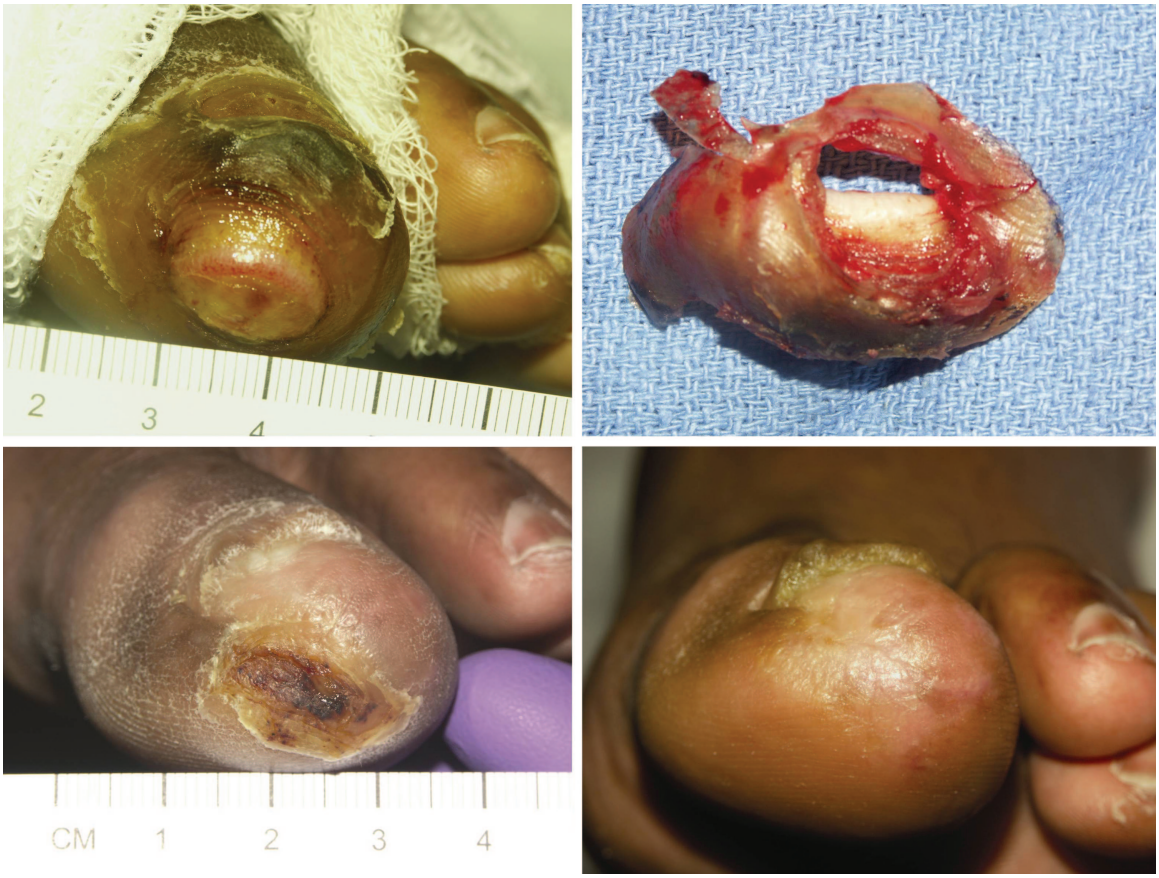

Fig. 2. (*Above, left*) This patient initially presented with a left first toe diabetic ulcer infected down to the bone. Though the open wound was small (1 × 1 cm), the surrounding callus was considerably larger, at approximately 4 × 2 cm. (*Above, right*) Wide surgical débridement that removed callus and extended into the surrounding soft integument was performed in the operating room. Interestingly, and atypically in these ulcers, in the pathology report of the sharply excised callus, the hyperkeratotic skin was called "hyperplastic." Pathologic analysis of the removed toenail showed focal bacteria and organisms consistent with fungus. (*Below, left*) Two months later during the healing process, a small callus developed that was immediately removed. (*Below, right*) The diabetic ulcer healed completely as a result of following the protocol. This patient typifies our expectation that even if a patient has poor glycemic control (this patient's hemoglobin A1c level was 12.7), healing should be expected and amputation avoided.

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 one third of patients with diabetes and is a source of extensive morbidity that can severely affect patient quality of life.[78–80] The toenails must always be treated, because untreated nails have an impaired ability to deter infection. Furthermore, it is important to emphasize that these toenails, which we routinely culture, often harbor bacteria. 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 diabetes, compared with those without diabetes.[81] 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.[82]

Treatment options for fungal toes include oral antifungal agents (e.g., griseofulvin, itraconazole, ketoconazole, terbinafine, and fluconazole), topical therapy (e.g., ciclopirox nail lacquer, 8%), and mechanical intervention.[83,84] Topical therapy is often preferred over systemic treatment, because there is less potential for serious adverse events and significant drug interactions.[85] How-

ever, topical therapy is often less effective. Mechanical intervention involves procedures that range from regular grooming of the nails to total surgical nail avulsion. Débridement 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.[86]

Assessment of Arterial Blood Supply

It is important to asses the pedal pulses of a patient with diabetes, and unless a pulse is clearly palpable, all patients with foot ulcers should undergo noninvasive vascular ankle-brachial index testing. In addition, all patients with diabetes older than 50 should be screened with an ankle-brachial index, whether or not they have an ulcer.[87] In most vascular laboratories, the index is measured by calculating the ratio of highest systolic pressure at the ankle divided by highest systolic pressure in the arm.[25,88,89] A normal ankle-brachial index is 0.9 to 1.3; a value less than 0.9 indicates peripheral arterial disease.[89] If the pulse volume is decreased or the index value is below 0.9, a vascular surgery consult should be obtained immediately.

Noninvasive laboratory tests frequently underestimate the severity of arterial disease in patients with diabetes, who commonly have a falsely elevated ankle-brachial index. In diabetes, atherosclerosis leads to severe arterial calcification and noncompressibility and results in index values well above normal (>1.30).[89] When arterial pressures are measured by Doppler echography with the 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, in some cases, 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 ankle-brachial index with a markedly dampened waveform suggests calcified vessels and a falsely elevated index value.[25]

If the patient has arterial insufficiency, revascularization (bypass) surgery or endovascular interventions may be necessary.[47,52,90,91] 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, called "small vessel disease." Distal arterial bypass grafting surgery to the pedal arteries is commonly practiced in patients with diabetes.[91,92]

Severe arterial occlusion is common among patients with diabetes, and contrast angiography remains the accepted standard for its assessment.[91] Magnetic resonance angiography images also demonstrate flowing blood and can be used successfully for anatomical evaluation of most arterial regions. Magnetic resonance angiography is able to image blood flow at velocities as slow as 2 cm/second, and it has been proven more accurate in diagnosing arterial disease than digital subtraction angiography.[93] Magnetic resonance angiography has been shown to be significantly better than digital subtraction angiography at disclosing peripheral runoff vessels in patients with diabetes.[94] Additional studies have reported that foot vessels that are not visualized on conventional angiography can be detected by magnetic resonance angiography, and these vessels were shown to be suitable target vessels for pedal bypass grafting.[93]

Special Considerations for Patients

Patients should be educated about self-management of diabetes, including how to check their feet for indications of wound formation. If such indications are found, patients should be examined immediately by a physician.[95] New ulcers usually appear as superficial lesions on the skin, and if they are identified early they can be successfully treated with negligible side effects. In addition, patients must be advised to obtain appropriate footwear that adequately protects the foot and sufficiently alleviates pressure.[2,96] Therefore, it is mandatory that every patient be evaluated for proper orthotics by an appropriately trained pedorthist.

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 drastically.[97–99] 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.[24]

Accurate assessment of the physiological impairments to healing in a chronic wound is essential when designing a successful treatment plan. The necessity for vascular intervention (e.g., 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 (e.g., spinal cord–injured and bed-bound patients) should be examined daily. Any new break in the skin in these patients requires immediate intervention.

OSTEOMYELITIS

Osteomyelitis is present in many diabetic foot ulcers, and it is treated most effectively by surgical removal of the infected bone.[100,101] After the infected bone is removed, the patient requires only antibiotics for control of bacteria in the surrounding soft tissues. This disease may be difficult to recognize if bony involvement is present at the time of débridement.[25] Demineralization, periosteal reaction, and bony destruction—the classic radiographic triad of osteomyelitis—appear only after 30 to 50 percent of bone has been destroyed, a process that takes up to 2 weeks.[102] 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 invasiveness, depending on the presence or absence of osteomyelitis.[103]

Several imaging techniques aid in determining whether diabetic patients have osteomyelitis, including image-guided bone biopsy,[103] magnetic resonance imaging,[102–106] three-phase bone scans,[103,104,107,108] leukocyte scans,[102–104,107,109,110] and computed tomography.[102,110,111] 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.[104]

With the availability of these diagnostic tools, early diagnosis is possible to facilitate successful treatment. Currently, there is no radiopharmaceutical imaging tool that is the accepted standard for assessing bone infection and inflammation.[112] Magnetic resonance imaging and bone biopsy are classically the preferred diagnostic tests for osteomyelitis in patients with diabetic foot ulcers,[113] with magnetic resonance imaging demonstrating the strongest evidence for accuracy of diagnosing osteomyelitis in the diabetic foot.[103,113] It has shown sensitivity of 84 to 92 percent and 84 percent specificity; bone probe has shown a 66 percent sensitivity and 85 percent specificity, and radiography has shown a 54 to 60 percent sensitivity and 80 percent specificity.[114–116] Bone probing has a positive predicative value of 89 percent, and if bone can be reached during an ulcer probe, no other tests are needed to diagnosis osteomyelitis. However, since a bone probe has a 56 percent negative predictive value, negative test results should be confirmed with alternate diagnostic modalities.[117] We recommend routine baseline radiographs. Any suspicion of osteomyelitis (e.g., nonhealing, palpable near bone) should be followed by a bone scan, magnetic resonance imaging, or a bone probe.

MANAGEMENT

Débridement

Débridement is essential in healing a diabetic ulcer.[24,25,27,118] Suitable débridement of the wound includes the removal of all surrounding calluses (including all hyperkeratotic tissue), necrotic tissue, and infected tissue (including bone) until a new border of healthy, bleeding soft tissue and uninfected bone is created.[25,119,120] Surgical débridement in the base should be completed until there is no scar or infection (even if down to the bone), with well-vascularized granulation tissue present; this has proved safe and therapeutic. The wound margins should be extended approximately 2 to 3 mm into healthy, bleeding, soft nonhyperkeratotic skin. A wide débridement is required to ensure removal of all hyperkeratosis. Débridement is not effective when it is not sufficiently wide; in this situation, the hyperkeratotic callous will likely reform. Ideally, one would consult a histologist to verify that the epithelium at the débrided wound edge has the same number of cell layers as one would expect in normal epithelium in the foot (three to four layers). Although the cells left behind are dysfunctional, thereby requiring additional therapies (e.g., off-loading, growth factors, and cellular therapies), alone or in combination, histologically, the cells should appear normal.

Débridement is necessary before application of other wound closure procedures and improves the outcome of the diabetic foot. Débridement causes activation of platelets to control hemorrhage and releases growth factors that begin the healing process.[25] After débridement, tissues should be kept moist to prevent formation of devitalized tissue and subsequent deepening of the wound. A moist wound environment also facilitates more rapid migration of keratinocytes across the wound bed. In addition, during débridement, it is important to take a deep culture and pathology samples.

Infection

Diabetic foot ulcers act as portals of entry for systemic infection (from cellulitis, infected foot ulcers, and osteomyelitis) and can have particularly deleterious effects on patients with diabetes,

whose impaired immunity increases their risk for local and systemic infection.[16,121,122] Clinical signs of infection include purulent secretions, two or more signs of inflammation (e.g., pain, redness, erythema, warmth, tenderness, and induration), foul odor, necrotic tissue, and a failure of a properly treated wound to heal.[123,124] If there is clinical evidence of infection, a bacterial culture should be obtained when a patient with a diabetic foot ulcer is first seen. A superficial wound swab is not a reliable identifier of bone bacteria.[125] A deep culture should be taken in nearly every patient with a diabetic foot ulcer who is not healing rapidly.

In one study of diabetic patients with limb-threatening foot infections, no statistical difference was observed between the two procedures in terms of species or frequency of isolation, suggesting that swabbing and deep tissue cultures are equally reliable for the initial monitoring of antimicrobial treatment.[126] However, in another comparative study, the mean number of microorganisms isolated by needle puncture was significantly lower compared with that obtained by superficial swabbing, suggesting that deep cultures are more specific than swab cultures, since superficial contaminants do not grow.[127] Furthermore, deep tissue culture may be more sensitive than swabbing for monitoring bacteria that have been selected for antibiotic resistance, such as microorganisms present in ulcers that remain infected after 30 days of antibiotic treatment.[126] With minimum complications, deep cultures should be considered for deep direct sampling in diabetic patients with osteomyelitis when surgical débridement is contraindicated or delayed.[127]

Infections in patients with diabetic foot ulcers are commonly polymicrobial and contain both aerobic and anaerobic bacteria.[24,125,128,129] Deep infections require early surgical débridement of all devitalized tissue, followed by antibiotic treatment to address the polymicrobial nature of the infection.[21] Deep cultures of infected tissue and bone should be taken during surgical débridement so that the most appropriate antibiotic therapy, taken orally or intravenously, can be given to the patient. When taking a deep culture, a blade is used to remove superficial tissue; after débridement to the level where the tissue appears viable and without scar or infection, an additional piece of tissue is then taken sharply with a knife or rongeur, and the specimen is sent for culture. We typically place the tissue specimen in a urine specimen jar.

Although antibiotics may be useful to treat superficial infections, they are often not sufficient to heal chronic wounds and, specifically, uncomplicated diabetic neuropathic forefoot ulcers.[23,24] Topical antimicrobial therapies (e.g., liquid silver nitrate, silver sulfadiazine, silver-coated dressings, and cadexomer iodine) have been shown to eliminate bacteria in diabetic foot ulcers.[130] Topical antiseptics, such as hydrogen peroxide, povidone, iodine, and acetic acid, are toxic to healing dermal cells and should be avoided.[21]

Parenteral antibiotics should be used to treat infections when there are residual bacteria in deep soft tissue and/or the presence of cellulitis and drainage. Oral antibiotics and outpatient management may not be successful in treating infected diabetic foot wounds because of insufficient tissue penetration. 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 infection is not improving.

Local bacterial contamination is always present in a nondébrided wound, and because of diabetic immune system impairments, sepsis can occur. Débridement 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.

OFF-LOADING

It has been established that minor traumas, such as repetitive stress and shoe pressure, are a significant component of the etiology in the pathway to ulcerations.[13,22] Peak plantar pressures are highest in the forefoot, compared with the rear foot and medial arch.[131] Reducing pressure applied to the wound, especially in the forefoot, is essential for optimal treatment.[13,95,132] 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.[24] Unrelieved pressure impairs healing and increases the risk of complications. The most studied and effective off-loading technique for treatment of neuropathic wounds, especially those midmost, is total contact casting,[25] which is considered the accepted standard for off-loading.[131] A total contact cast 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.[133] Although this method is extremely suc-

cessful for treating diabetic foot ulcers, not all diabetic foot ulcers are candidates for casting. Frequent wound inspection and daily dressing changes are not possible, which renders these casts unsuitable for ischemic ulcers. Total contact casting also requires experienced technicians who are trained specifically in this application. When the cast is applied inappropriately, there is a risk of the ulcer worsening and an infection being missed. Many new off-loading modalities are being investigated, because of the drawbacks of total contact casting. Two examples are removable cast walkers and half-shoes.[131] A new technique takes a removable cast walker and renders it irremovable by wrapping it with cast material.[134,135] We recommend these three alternatives to the total contact cast.

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 that are designed to decrease the magnitude of pressure, friction, and shear, while providing appropriate levels of moisture and temperatures that support tissue health and growth, should also be used.

Objective Wound Measurement

At least once a week, the length and width of the wound must be measured in all patients. Planimetry is optimal, but if it is 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. Sequential measurements of wound area are helpful in measuring the healing of diabetic foot wounds and evaluating the effectiveness of therapeutic treatment.[136–138]

Wound Bed Preparation

The goal of wound bed preparation is to have well-vascularized granulation tissue with no adjacent cellulites, drainage, or odor.[139] Removal of scar tissue is also essential.[140] Proper débridement concurrently prepares the wound bed and stimulates the healing process.[25] Optimal wound bed preparation includes stimulation of granulation tissue (new collagen and angiogenesis) and new epithelialization, with the goal of elimination of bacteria in the wound.[120] Furthermore, it is important to treat the underlying pathophysiology.[141] After débridement of an infected wound, topical antibiotics may be efficacious. The silver cation has been shown to be effective at killing the antibiotic-resistant strains of bacteria. Different types of topical silver applications include liquid silver nitrate, silver sulfadiazine (in a cream form), and silver-coated dressings.[142] Cadexomer iodine also utilizes sustained release of the antimicrobial agent, which results in removal of both the bacteria and exudates.[143]

Dressings

After débridement, tissues should be kept moist to prevent formation of devitalized tissue and subsequent deepening of the wound.[118] A moist wound facilitates more rapid migration of epidermal cells across the wound bed, which promotes angiogenesis and connective tissue synthesis.[144] 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 that is actively granulating requires a dressing material different from that used in the epithelializing phase of healing; a deep sinus wound should be treated differently from a wound that produces copious amounts of exudates.[141]

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.[24]

In the past decade, the 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.[23]

Biological Therapy

The treatments discussed in the following sections (e.g., bilayered keratinocytes and fibroblasts

and platelet-derived growth factor-BB) must be used when patients fail to improve after the approaches described above have been applied for 3 weeks. We recommend the implementation of biological therapy if wound size cannot be decreased by more than 10 percent within a 3-week time period. It should be emphasized that these two therapies are the only U.S. Food and Drug Administration–approved topical agents in randomized clinical trials.

Diabetic foot ulcers exhibit a decreased angiogenic response and a decreased production of growth factors within the wound. Cell therapy, also known as biological therapy, presents an appropriate treatment option in some cases. Biological therapy is an ideal treatment for diabetic foot ulcers, because it adds cells that release growth factors to a growth factor-dependent environment, increases cytokines and matrix proteins, and promotes angiogenesis.[20,145] Accelerating healing time decreases the risk of wound infection.

The biological therapy available today is 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.[146] The bilayer cell therapy has been shown to increase the healing rate of diabetic foot ulcers by 55 percent. Later studies that provided optimal diabetic foot ulcer care and controlled for patient's comorbidities showed that the cellular therapy results in 100 percent healing of all diabetic foot ulcers not complicated by osteomyelitis or ischemia.[147] This cell treatment has also been proved effective in treating ulcers that have resisted standard therapy (e.g., venous ulcers[148] and pressure ulcers[26]). Fibroblasts synthesize collagen and secrete a mixture of growth factors and matrix proteins in physiological concentrations essential for wound healing and epithelialization.[149] Keratinocytes secrete substances that stimulate target genes, which control the cellular activation cycle responsible for the wound-healing process. Biological therapy is used following débridement after complete hemostasis is attained. A nonadhering sterile dressing is then placed over the wound, followed by petroleum jelly and an occlusive dressing. This procedure can be performed easily in the outpatient, inpatient, or nursing home setting. Often wounds require several applications, as the biological effect from the cell therapy lasts only up to 6 weeks.

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.[147]

Growth factors applied topically to wounds can accelerate healing by stimulating granulation tissue formation and enhancing epithelialization.[25] 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 (recombinant human PDGF-BB) is a homodimer produced through recombinant DNA technology. Becaplermin contains the B chain of human PDGF (PDGF-BB), and its biological activity is similar to that of naturally occurring PDGF (e.g., promoting chemotactic recruitment and proliferation of cells involved in the wound repair process).[150] 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 an innovative, pharmacologically active treatment for chronic lower extremity diabetic ulcers. Becaplermin gel is easy for patients or their caregivers to apply in a nonformal clinical setting, and published studies have shown that it has an excellent safety profile.[150–152]

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-moistened gauze dressing. The becaplermin is gently rinsed off 12 hours later and replaced with saline-moistened gauze (without reapplication of the gel), or administration of the gel is repeated. The dressing is changed 12 hours later, with reapplication of the gel; the cycle is repeated in 12-hour intervals.[24] Further study is required to determine the optimal concentration of becaplermin gel on diabetic foot ulcers for optimal healing.

Negative Pressure Wound Therapy

Recent evidence from a controlled trial of negative pressure wound therapy using the vacuum-assisted closure device (V.A.C.; KCI, Inc., San Antonio, Texas) suggests that in complex postoperative wounds in the diabetic foot, more rapid healing

occurs when compared with standard treatment.[153] Thus, this therapy should be considered in large foot ulcers and particularly postlocal amputation wounds, when as above, satisfactory healing is not occurring after a 3-week implementation of the protocol.[22,154] For patients who ambulate, negative pressure wound therapy units can be worn around the waist that allow patients the freedom of movement to perform daily activities.[22] Utilizing a removable cast walker and a modified negative pressure dressing may not impart a clinically significant amount of increased pressure to the plantar aspect of the diabetic foot.[155]

Reconstructive Therapies

Reconstructive therapies may be useful treatment options when the area of the diabetic foot ulcer has not decreased by more than 10 percent after the above approached have been applied for 2 months. Plastic surgery has shown high complication rates, but studies have also suggested that in some situations, reconstructive therapies (e.g., meshed and split-thickness skin grafts and local and free muscle flaps) may be efficacious in preventing amputations.[90,156–159] In one study, reconstructive therapeutic procedures had at the time of discharge a 71 percent, 50 percent, and 33 percent rate of healing of stage II, III, and IV diabetic foot wounds, respectively.[158] In another study of soft-tissue reconstructive surgery for diabetic foot ulcers, where 52 percent of patients presented with osteomyelitis and 42 percent of the affected limbs required revascularization before reconstruction, 84 percent of the wounds healed.[159] In a third study, local flap surgery of noninfected and well-perfused diabetic foot ulcers showed a 97 percent rate of healing.[90]

WOUND ELECTRONIC MEDICAL RECORD

The wound electronic medical record is a secure, Internet-based, point-of-care informatics system that integrates patient medical and treatment histories with digitalized photographs of skin wounds. This digital datasheet contains the clinical data pertinent to wound healing, including real-time graphs of wound healing (e.g., wound length, width, depth, and area over time); hematology and chemistry laboratory data; radiology and pathology results; drug sensitivities to wound microorganisms; wound treatment and débridement history; concurrent systemic medications; objective wound evaluation assessments of drainage, pain, and redness in the area surrounding the wound; and digitized close-up photographs taken weekly to record wound-healing progress. The wound electronic medical record incorporates photographs as standardized, objective records of wound healing. It also stores the patient's medical history, surgical history, vascular studies, and contact information for the patient's primary care doctor. Having to include all this information about the patient in the database ensures that the protocol described herein is followed.

The wound electronic medical record includes wound and medical information necessary to make informed clinical decisions, and it presents these data in a clear, comprehensive, and easily understood form. This allows the wound-healing practitioner to view the necessary medical information efficiently and in real time. The wound electronic medical record is a valuable diagnostic tool that can potentially increase the level of patient care for patients with diabetic foot wounds, promoting healing of ulcers and reducing amputation rates by alerting clinicians to wound progression or failure to heal. A fundamental problem in implementing diabetic foot wound treatment protocols is the difficulty of assigning accountability for the condition of the wound. With the wound electronic medical record, provided a patient has not recently been débrided, if the database demonstrates that a patient's wound area is increasing, this information is disseminated among all the health care providers, thereby guaranteeing a change in treatment plan. In addition, in instances when a wound that initially responds well to a particular treatment gradually grows less responsive to that same treatment over time, the wound electronic medical record alerts all clinicians to changes in response to treatment earlier than otherwise may have been noticed.

COMPREHENSIVE WOUND CENTER

The integrated wound center is an increasingly common occurrence in both Europe and the United States.[160] Communication is one of the biggest impediments to implementing a standardized protocol such as the one outlined in this report. Although diabetic foot wounds are often treated by a single medical provider, the complex nature of wound healing calls for the close collaboration of specialists dedicated to each ailment.[160,161] An ideal wound center provides the requisite collaborations for optimal healing, including both inpatient and outpatient care, general medicine, podiatry, general surgery, vascular surgery, infectious disease, orthopedics, diabetol-

ogy, nutrition, orthotics, radiology, and neurology. These centers streamline protocol implementation, cost effectiveness, and the achievement of optimal performance from the devices used.[161] Because not every program can afford to build a wound center, implementation and enforcement of a protocol presents an effective alternative in a modest family practice physician's office. Although implementing a protocol will decrease the number of amputations performed, the logistics of it will always depend on the clinicians and resources available. In practical terms, this may or may not require subsidization by the hospital. The urgency of decreasing amputations requires such partnerships.

CONCLUSIONS

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.

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