The prevalence of diabetes mellitus is increasing worldwide; by the year 2025, an estimated 300 million people will have diabetes.1 Diabetic foot ulcers (DFUs), one of the most common complications of diabetes, have an annual incidence rate of 1% to 4% and a lifetime risk of 15% to 25%.2-5 Peripheral neuropathy is a major contributing factor in the development of DFUs, along with deformity, callus, trauma, and vascular insufficiency.1,4,6,7 DFUs are often recalcitrant to treatment and associated with serious medical complications, such as osteomyelitis and lower limb amputation. Approximately 15% of DFUs result in lower extremity amputation.5,7 More than 85% of lower extremity amputations in patients with diabetes are precipitated by a foot ulcer.6,8

The ultimate goal of DFU management is complete wound healing. Standard management strategies for healing DFUs typically have included debridement, infection control, offloading, and the use of dressings to maintain a moist wound bed. Despite the use of standard management strategies, healing rates of DFUs remain low.

The purpose of this review is to enhance understanding of the effect of DFUs on quality of life (QoL), costs, morbidity, and mortality and to describe current management approaches to optimize outcomes of care.

The Effects of Diabetic Foot Ulcers

Quality of life. DFUs can be painful and limit daily and social
activities, leading to reduced QoL. Goodridge et al.9 compared QoL parameters in 104 patients with healed and unhealed DFUs (defined as having a history of DFU ≥ 6 months) who received care in a tertiary foot care clinic. The results of each DFU group also were compared with patients with diabetes and no history of a foot ulcer, patients with hypertension, and persons in the general population. Results using the Medical Outcomes Survey Short Form 12 questionnaire showed the unhealed DFU group had a greater reduction in overall physical health compared with patients with diabetes and no history of ulcer, patients with hypertension, and persons in the general population than the healed DFU group. Additionally, significantly reduced QoL scores were found in the unhealed DFU group compared with the healed DFU group in several measures of physical health (P < 0.002 to P < 0.04). Patients with unhealed DFUs experienced significantly greater physical limitations and pain that affected their daily activities and interfered with their social lives (see Figure 1). Results of the Cardiff Wound Impact Scale showed patients with unhealed ulcers experienced frustration and anxiety associated with their wounds, had difficulties with activities of daily living and footwear, and complained of having a limited social life.

**Costs.** A retrospective cohort study7 using data collected from a health maintenance organization from 1993 to 1995 found that patients with DFUs (N = 514) used significantly more healthcare resources (P < 0.001) than age- and sex-matched control subjects with diabetes and no history of foot ulcers. In the first year after DFU diagnosis, patients with ulcers had 0.24 more emergency room visits, 22 more outpatient visits, and 4.6 more inpatient days than the control patients. In the second year, emergency room visits remained unchanged for the DFU group, but outpatient visits and inpatient days declined. The year 2 data for the control group remained unchanged in all categories. Of the 514 patients with DFUs in the study, 15% developed osteomyelitis and 15.6% had a lower limb amputated. At 36 months postdiagnosis, survival was significantly decreased for the DFU group compared with the diabetic control group (72% versus 87%, respectively; P < 0.001).

The study7 also found the attributable cost of treating a new DFU for the 2-year period after diagnosis was $27,987 (in 1995 US dollars). Based on the medical care component of the US consumer price index, which measures the average change in prices over time of goods and services purchased by households, that cost has increased to $45,301 (in 2008 US dollars).10 The high cost of treatment is linked to the high rate of healthcare utilization among patients with DFUs.7

**Mortality.** The high rate of mortality in patients with DFUs is well known, but how it compares with other serious medical conditions is less well understood. Armstrong et al.11 discussed the relatively high 5-year mortality rates for patients with neuropathic and ischemic DFUs and diabetes-related amputations compared with serious medical conditions, including several common types of cancer, using data gathered from multiple sources. By 5 years, 45% to 55% of patients with neuropathic and ischemic DFUs, respectively, will die. These common complications of diabetes have higher mortality rates than cancers of the prostate, breast, and colon, as well as Hodgkin’s disease (see Figure 2). Peripheral arterial disease itself, a primary contributor to the development of ischemic DFU, is associated with a high mortality rate.

A recent 10-year, prospective, population-based study12 has found a history of DFU to be a significant independent predictor of mortality in patients with diabetes. Findings are based on data from 1,339 patients with diabetes with a history of DFU, 155 patients with diabetes without a history of DFU, and 63,632 nondiabetic participants in the Nord-Trøndelag Health Study in Norway. The 10-year mortality rate for patients with diabetes with a history of DFU was 49% compared...
with 35.2% for patients with diabetes and no history of DFU and 10.5% for nondiabetics. Among the diabetic subjects, DFU history was associated with a 38% increased risk of death. The association between DFU history and mortality did not change substantially after accounting for cardiovascular disease, microalbuminuria, anxiety, or depression.

**Healing rates.** According to the 1999 American Diabetes Association consensus statement on DFU care, DFUs are believed to become chronic wounds because of predisposing factors of diabetes, such as peripheral neuropathy, abnormal cellular function, and vascular disease leading to tissue hypoxia. The reason some ulcers do not progress from an inflammatory/proliferative phase is not well understood, but studies of chronic ulcers have found excessive activity of the matrix metalloproteinases collagenase and elastase that results in premature degradation of collagen and growth factors.

DFU healing rate was examined in a meta-analysis of 10 control groups from US Food and Drug Administration (FDA)-approved clinical trials that used standard wound care, defined as debriding, offloading, and saline-moistened gauze dressings or placebo gel and gauze dressings. The weighted mean rates of neuropathic ulcer healing were 24.2% (95% confidence interval [CI] 19.5%, 28.8%) over 12 weeks and 30.9% (95% CI 26.6%, 35.1%) over 20 weeks. These data offer clinicians and patients realistic expectations of the chance of healing neuropathic foot ulcers in patients with diabetes is a challenge.

**Debridement.** Removing necrotic and devitalized tissues is an important first step in the treatment process. In addition to debris removal, debriding helps rid the wound of bacteria. Surgical debridement with a sharp instrument (e.g., a scalpel) is considered the gold standard technique (Level I evidence) but more than one debridement technique (e.g., ultrasound, pulsed lavage, and autolytic and topical enzymatic ointments) may be appropriate.

Debridement is thought to change the wound physiology from chronic to acute. There is evidence that frequent surgical debridement of wound necrotic tissue and callus surrounding DFUs leads to higher rates of healing. A prospective, randomized, double-blind multicenter, clinical trial evaluated patients with chronic (defined as ≥8 weeks duration), neuropathic DFUs (N = 118) treated with recombinant human platelet-derived growth factor-beta beta or placebo. Across the six treatment centers, patients who received frequent debridement experienced a higher rate of healing than patients who received less frequent debridement, regardless of whether they received active treatment or placebo (see Table 1). Results from these studies demonstrate that frequent debridement is an important first step in wound care for DFUs, irrespective of other wound treatments used.

**Proper debridement technique is necessary for optimal reduction of bacteria, debris, and devitalized tissue (Level II evidence).** During debridement, the necrotic tissue is excised to the level of healthy, bleeding tissue. Encompassing callus or Medicare and Medicaid Services (CMS) consensus guidelines for chronic wounds and include clinical as well as pre-clinical studies. Additionally, each guideline is graded by the strength of the supporting evidence — i.e., a Level I guideline, the highest grade, is based on a meta-analysis of multiple randomized controlled trials (RCT) or at least two RCTs and a Level II is based on at least one RCT and two significant clinical series or expert opinion papers.

The WHS guidelines comprise eight categories beginning with diagnosis of the ulcer and ending with prevention of recurrences. Optimal DFU therapy includes debridement of necrotic and devitalized tissue, use of moist dressings, controlling infection, and using off-loading techniques to reduce pressure on the wound. These standard principles are ubiquitous in DFU guidelines. However, the WHS guidelines and other recent reviews advocate a re-evaluation of the treatment regimen and considering the use of advanced-care agents (topical, device, or systemic) for wounds with a 4-week treatment history of standard wound care resulting in <50% overall wound area reduction.

**Standard of Wound Care for Diabetic Foot Ulcers**

To better address the challenges of healing DFUs, in 2006 the Wound Healing Society (WHS) published evidence-based treatment guidelines. These guidelines were written using existing medical literature databases as well as the Medicare/Center for Medicare and Medicaid Services (CMS) consensus guidelines for chronic wounds and include clinical as well as pre-clinical studies. Additionally, each guideline is graded by the strength of the supporting evidence — i.e., a Level I guideline, the highest grade, is based on a meta-analysis of multiple randomized controlled trials (RCT) or at least two RCTs and a Level II is based on at least one RCT and two significant clinical series or expert opinion papers.

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Urgent debridement is often the first step in changing the wound environment because microorganisms thrive on devitalized tissue. In DFUs, polymicrobial infections are a primary cause of overwhelming the host’s ability to mount a successful defense. Clinical signs of infection in DFU often do not become evident until the underlying tissue or bone is affected and a systemic inflammatory response is activated. Clinicians must vigilantly assess subtle, secondary signs of infection in patients with DFU and rigorously treat suspected infections.

Optimal treatment decisions can be made only after determining the causative organism. Tissue cultures have remained the gold standard of bacterial identification for many years. Deep tissue specimens produce better results than superficial swabs, especially when osteomyelitis is suspected (Level II evidence). However, cultures may not be accurate if the sampling technique was poor or if the patient was receiving antibiotic treatment at the time of sampling. Additionally, cultures can take up to 48 hours to develop.

Although some investigators do not favor superficial swabs, Gardner et al conducted an observational, cross-sectional clinical trial studying the Levine swabbing technique, a quick and simple quantitative swab culture method, in tissue exudate of patients with DFU and rigorously treat suspected infections.

**Table 1. Relationship between debridement frequency and ulcer healing (N = 118)**

<table>
<thead>
<tr>
<th>Study site</th>
<th>rhPDHF group</th>
<th>Placebo group</th>
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<tr>
<td></td>
<td>% Office visits with debridement</td>
<td>% Patients whose ulcer healed</td>
</tr>
<tr>
<td>1</td>
<td>15</td>
<td>20</td>
</tr>
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<td>2</td>
<td>33</td>
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<td>3*</td>
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<td>6</td>
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*Pooled data from five sites. Reproduced with permission rhPDHF = recombinant human platelet-derived growth factor

Infection control. Theoretically, all wounds are at risk of microbial colonization because the balance between host and endogenous microflora has been disrupted. Colonization of a wound causes changes in the wound environment that encourage the growth of other pathogenic and competing microorganisms. Wounds typically become infected with endogenous bacteria that become pathogenic in a wound environment, overwhelming the host’s ability to mount a successful defense. In DFUs, polymicrobial infections are a primary cause of chronic inflammation. Additionally, polymorphonucleocytes (inflammatory cells essential to normal wound healing) are believed to become hyperactivated in DFU and play a key role in chronic inflammation. For these reasons, debridement is the first step in changing the wound environment because microorganisms thrive on devitalized tissue.

Infection control is of paramount importance in DFU treatment because infection is strongly associated with amputation. Lavery et al’s large, prospective cohort study of 1,666 patients with diabetes found that foot infection increased the risk of amputation by 154.5 times (95% CI, 58.5–468.5; P < 0.001).

Ulcers should be closely monitored for signs or symptoms of infection. If the wound exhibits pus, redness or change in skin color, inflammation or swelling, pain, tenderness or warmth, or delayed healing, or if the patient develops a fever, infection should be suspected. Lavery et al prospectively determined risk factors for infection of DFU by monitoring patients with diabetes over 2 years. During the study, 9.1% of the patients developed one or more infected DFUs — most were soft tissue infections but 19.9% of patients with foot infection developed osteomyelitis. Statistically significant (P < .05 each) and independent risk factors for infection included wounds that penetrated to the bone, had a >30-day duration, a traumatic etiology, were recurrent, and occurred in patients with peripheral vascular disease (see Table 2).

However, many people with diabetes do not develop obvious clinical signs of infection even when the microbial load in the wound or blood is high because hyperglycemia and peripheral vascular disease reduce the inflammatory response to infectious agents. Clinical signs of infection in DFU often do not become evident until the underlying tissue or bone is affected and a systemic inflammatory response is activated. Clinicians must vigilantly assess subtle, secondary signs of infection in patients with DFU and rigorously treat suspected infections.

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Although some investigators do not favor superficial swabs, Gardner et al conducted an observational, cross-sectional clinical trial studying the Levine swabbing technique, a quick and simple quantitative swab culture method, in tissue exudate of patients with nonarterial, full-thickness, chronic wounds (N = 83). Culture findings based on swab specimens using the Levine technique and specimens of viable wound tissue were assessed. The swab results showed the Levine technique had 90% sensitivity and 57% specificity at a critical threshold of 37,000 organisms per swab. The mean concordance between swabs and tissue specimens was 78%. These results indicate the Levine technique is a fairly accurate measure of the number of bacteria in the wound.

Newer but not universally available diagnostic tests with greater sensitivity have been developed that can better identify infections or pathogens within hours instead of days. For instance, a polymerase chain reaction assay can detect Gram-
positive, Gram-negative, and anaerobic organisms. An oligonucleotide array can detect genes involved with resistance and toxins and also can identify some specific species by their genotype. Finally, magnetic resonance imaging (MRI) is an emerging technique for detecting infections in soft tissue and bone.

Infections in DFUs are usually polymicrobial, predominantly comprising aerobic, Gram-positive, cocci organisms.22 Staphylococcus aureus is the most common pathogen found in DFUs.20,22 Notably, the number of methicillin-resistant S. aureus (MRSA) infections is increasing.22 Polymicrobial infections also may include aerobic Gram-negative bacilli or obligate anaerobes.22

Level II evidence15 indicates acute DFUs typically respond to systemic antimicrobial agents. To date, the FDA has approved linezolid, eratapenem, and piperacillin/tazobactam for the systemic treatment of DFU infections not complicated by osteomyelitis.22 More than 50 other antibiotics are available to treat complicated skin and skin structure infections. Level I evidence15 has shown that topical antimicrobial agents have better efficacy than systemic agents for the treatment of chronic DFUs; this is because systemic antibiotics do not have adequate penetration to affect bacterial levels in the granulation tissue of chronic wounds.26 A number of new topical and local antimicrobial agents such as silver-based products, iodides, peptides, and superoxidized water solutions have been developed to treat DFU infections. However, the efficacy of these agents has not been established in randomized, controlled trials.22

Osteomyelitis often underlies an infected DFU. The bone can be cultured but less invasive diagnostic techniques are available, such as x-ray, MRI, or computed axial tomography scans (Level II evidence).15 Osteomyelitis can be difficult to cure. The bone should be debrided and a 2- to 4-week course of antibiotic therapy should follow. In some cases, six or more weeks of treatment may be necessary (Level II evidence).15

Offloading. The pressure-relieving technique known as offloading is essential for maximizing DFU healing (Level I evidence).15 Offloading methods include total, non-weightbearing methods (bedrest, crutches, and wheelchairs) and specialized footwear (boots, surgical shoes, half-shoes, and sandals); devices such as the removable cast walker (RCW) and total contact casting (TCC) also may be effective (Level II evidence). Among offloading modalities, TCC is associated with increased rates of healing and faster healing; however, it is not recommended for patients with ischemic or infected wounds.13

Armstrong et al27 prospectively evaluated healing rates of uninfected, nonischemic, neuropathic plantar foot ulcers in patients with diabetes (N = 63) treated with one of three offloading modalities. The proportion of healed ulcers after 12 weeks was greatest in the TCC group (89.5% of patients), followed by the RCW (65.0%) and half-shoe (58.3%) groups. A significantly greater proportion of healed ulcers occurred in the TCC group compared with the other offloading modalities (89.5% versus 61.4%, \( P = .026 \); OR, 5.4; 95% CI, 1.1–26.1). Significantly faster healing rates favored TCC compared with RCW (\( P = .033 \)) and the half-shoe (\( P = .012 \)).

Although some data indicate equivalence in offloading efficacy between RCW and TCC,28 compliance rates favor the TCC. In a prospective, longitudinal study that evaluated RCW compliance in 20 patients with DFUs, Armstrong et al29 found that patients wore their RCW during only 28% of daily activities each day. This lack of compliance may explain the poor clinical trial results for offloading devices and perhaps other treatment studies. These results suggest that offloading devices that cannot be easily
removed may lead to improved healing of DFUs. To test this theory, Armstrong et al. randomly assigned 50 patients with DFUs to wear an RCW or an “instant TCC” (iTCC), which was an RCW wrapped with a cohesive bandage that made it difficult to remove. After 12 weeks of treatment, 82.6% of the ulcers in the iTCC group had healed compared with 51.9% in the RCW group ($P = .02$; OR 1.8; 95% CI: 1.1–2.9). The rate of healing was significantly faster in the iTCC group than in the RCW group (41.6 ± 18.7 days versus 58.0 ± 15.2 days, $P = .02$). Thus, in “real-world” settings, the iTCC is more effective than the RCW at improving rates of healing because of the increased rate of compliance.

**Four treatment weeks/50% improvement rule.** At the 1999 Consensus Development Conference, the American Diabetes Association stated, “Any wound that remains unhealed after 4 weeks is cause for concern, as it is associated with worse outcomes, including amputations.” Based on this statement, in a prospective, multicenter trial of patients with DFUs ($N = 203$), Sheehan et al. assessed whether a 50% wound area reduction after 4 weeks of standard wound care (ie, debridging at weekly intervals, offloading, and moist dressings) and either a collagen/oxidized regenerated cellulose dressing or moistened gauze predicted complete healing within a 12-week period. The mean percent reduction in ulcer area after the first 4 treatment weeks was significantly increased for “healers” (defined as patients with complete healing within 12 weeks) compared with patients without complete healing (see Figure 3a). A significantly greater proportion of patients ($P < 0.001$) whose ulcers healed above the midpoint criterion (defined as 53% wound area reduction) at week 4 were completely healed by week 12 compared with patients whose ulcers did not heal to the midpoint criterion at week 4 (see Figure 3b). These data suggest that achieving a 50% reduction in wound area after 4 weeks of standard wound care can strongly predict which patients will heal and which patients are unlikely to heal.

In a clinical practice review of neuropathic DFUs, Boulton et al. noted, “… the failure to reduce the size of an ulcer after 4 weeks of treatment that includes appropriate debridement and pressure reduction should prompt consideration of adjuvant therapy.” Several types of advanced-care technologies are available and help promote the healing of chronic ulcers. The WHS guidelines advise the selective use of advanced-care agents — topical, device, and/or systemic — when healing fails to progress in response to traditional therapies.
**Advanced-Care Therapies**

According to the WHS guideline, platelet-derived growth factor is effective in treating DFU (Level I evidence) and isolated reports suggest that other cytokine growth factors also may be useful. Negative pressure wound therapy (NPWT), electrical stimulation, hyperbaric oxygen, and living skin equivalents (bioengineered skin containing live dermal cells) also may be of benefit (Level I evidence).15

Of the currently available advanced-care treatments, living skin equivalents may be of particular benefit in healing DFUs. In their review of a living dermal substitute and the optimal treatment strategy for diabetic foot ulcers, Armstrong et al18 concluded, “Arguably, the use of an active therapy, such as a bioengineered skin substitute to stimulate healing in nonresponding wounds after 4 weeks of treatment, is the optimal care in 2007.” Living skin equivalents undergo the FDA’s most rigorous medical device approval process. To gain premarket or biologic license application approval, living skin equivalents must demonstrate efficacy and safety in well-controlled clinical trials.23 The continued application of standard wound care is required for optimum response with advanced-care therapies.34

Cost-effectiveness studies of advanced-care agents for DFUs have been conducted. In a comprehensive review of nine studies published in peer-reviewed, English-language journals, Chow et al16 evaluated the cost-effectiveness of advanced-care agents, including becaplermin (Regranex®, Otho-McNeill, Raritan, NJ), topical gel containing recombinant human PDGF, and two living skin equivalents: a bilayered skin substitute (Aplicraf®; Organogenesis, Inc., Canton, MA) and a human fibroblast-derived dermal substitute (Dermagraft®, Advanced BioHealing, Inc., La Jolla, CA) using the published data to calculate costs. All studies reported increased effectiveness of advanced-care agents compared with wound care that typically consisted of the application of saline-moistened dressings; however, the cost-effectiveness results were different across studies. Costs of care varied based on the study year, design, and currency used. Higher costs of using living skin equivalents were found to be attributable to the increased time associated with applying the skin equivalent compared to the time needed to apply saline-moistened dressings. However, the higher costs associated with the advanced-care agents often were offset by the avoidance of serious adverse events and resections or amputations.

The studies reviewed had important limiting factors. First, the cost-effectiveness results may not be generalizable because of differences in treatment costs and general wound care guidelines across countries where the studies were conducted. Additionally, the studies were of short duration (12 weeks to 6 months), necessitating extrapolation of the results. These authors and others have concluded that long-term cost-effectiveness studies of living skin equivalents are warranted.16,34

A cost-effectiveness study35 compared a living skin equivalent plus standard wound care to standard wound care alone in patients with DFUs (N = 208) using data from a 1-year, large, prospective, well-controlled clinical trial and published healthcare resource studies. In this study, standard wound care included debridement, offloading, and application of moist dressings. Cost effectiveness was estimated using a Markov simulation model. The number of living skin equivalent applications ranged from one to four, delivered within the first 4 weeks of treatment. Over the 1-year period, the group that received living skin equivalent plus standard wound care had 12% lower costs, 24% more ulcer-free days, 67% less time with an infected ulcer, and 63% lower risk of amputation than the group that received standard wound care alone. When looking at the costs over the entire 1-year span, for the first five study months, costs were higher for the living skin equivalent group due to the initial cost of application. Costs became equivalent between groups at treatment month 5, followed by decreasing costs for the living skin equivalent group through month 12. For 1 year of treatment, the cost of the living skin equivalent was $4,371 compared with $4,985 (1999 US dollars) for standard wound care alone. An important strength of this study is that standard wound care was similar to that recommended by current guidelines (offloading, debridement, and moist dressings) and not merely the application of saline-moistened dressings as was performed in the studies reviewed by Chow et al.16

**Conclusion**

DFUs are a common complication of diabetes mellitus and associated with a high rate of morbidity, healthcare utilization, and costs; serious complications, including osteomyelitis and amputation; impaired QoL; and a high rate of mortality. Preventing and healing DFUs remains a challenge due to medical conditions associated with diabetes mellitus, such as peripheral neuropathy and vascular insufficiency; reported proportions of ulcers healed range from 24%14 to 82%27 after 12 weeks of care. Most practice guidelines for management of DFU have defined standard wound care as weekly debridement of necrotic tissue, infection control, offloading to relieve pressure, and maintenance of a moist wound bed. Additionally, newer comprehensive evidence-based guidelines advocate the use of advanced-care agents, such as living skin equivalents, for chronic ulcers (ie, <50% wound reduction after 4 weeks of standard wound care). It is believed that wide utilization of these guidelines will reduce diabetes-related healthcare costs and the prevalence of DFUs, diabetes-related amputations, and premature death in patients with diabetes mellitus.

Although advancements in the care of DFUs have occurred in recent years, further research in this field is much needed. Additional prospective clinical trials of advanced-care therapies as well as continued research into mechanisms of action and methodologies to improve physician and patient adherence to

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optimal wound management are needed, especially in light of the age of some of the guidelines and the increasing emphasis on evidence-based practice despite a lack of safety and efficacy data. Creating new evidence-based protocols has the potential to facilitate expedient, prudent use of emerging technologies, shedding new light on old wounds.

References