Wound-Healing Protocols for Diabetic Foot and Pressure Ulcers

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ABSTRACT

Diabetic foot and pressure ulcers are chronic wounds by definition. They share similar pathogeneses; i.e., a combination of increased pressure and decreased angiogenic response. Neuropathy, trauma, and deformity also often contribute to development of both types of ulcers. Early intervention and proper

treatment should result in complete healing of non-ischemic diabetic foot and pressure ulcers, as defined by 100% epithelialization and no drainage (if no osteomyelitis is present). We developed the following paradigm, which has proved to be highly effective for complete healing of these wounds: 1) recognition that all patients with limited mobility are at risk for a sacral, ischial, trochanteric, or heel pressure ulcer; 2) daily self-examination of the sacrum, ischium, buttocks hips, and heels of all bed-bound patients and the feet of patients with diabetes with risk factors (e.g., neuropathy); 3) initiation of a treatment protocol immediately upon recognition of a break in the skin (i.e., emergence of a new wound); 4) objective measurement by planimetry of every wound (at a minimum, weekly) and documentation of its progress; 5) establishment of a moist wound-healing environment; 6) relief of pressure from the wound; 7) debridement of all non-viable tissue in the wound; 8) elimination of all drainage and cellulitis; 9) cellular therapy or growth factors for patients with wounds that do not heal rapidly after initial treatment; and 10) continuous physical and psychosocial support for all patients. If this paradigm is followed, most diabetic foot and pressure ulcers are expected to heal.

INTRODUCTION

The morbidity and mortality that result from diabetic foot and pressure ulcers (sacral, gluteal, trochanteric, or heel) present a healthcare problem of epidemic proportions. Not only are these chronic wounds associated with high rates of morbidity (Table 1); they also are extremely expensive, both to the patient and society (Table 2), and have a profound effect on the patient's quality of life. The severe physical, economic, social, and mental burdens these wounds impose on patients mandate a comprehensive and systematic approach to wound healing.

WOUND HEALING: ACUTE AND CHRONIC WOUNDS

Wounds can be divided into two categories: acute and chronic. Acute wounds heal in an orderly and timely manner, and result in sustained restoration of anatomic and functional integrity.[1] A chronic wound, however, fails to heal in a timely and orderly process due to a physiological impairment, and ultimately compromises anatomic and functional integrity.[2] Diabetic foot and pressure ulcers are both products of underlying physiological impairments and are, by definition, chronic wounds from the moment they first occur. These ulcers always require immediate intervention to prevent progression to a more complicated and potentially morbid wound.

INCIDENCE AND PATHOGENESIS

Diabetes and pressure can cause impairments in microvascular circulation that result in changes in the skin of the lower extremities, which potentially lead to diabetic foot ulcers and subsequent infection. Specifically, the effects of high blood glucose concentration may worsen ischemia and tissue injury.[3,4]

Pressure ulcers present a major healthcare problem. Pressure ulcers are common in patients with spinal cord injuries, major orthopedic reconstruction, or who are otherwise bed-bound or use wheelchairs. Studies demonstrate that between 3% and 11% of all hospitalized patients suffer from pressure ulcers.[5-13] At least 9.5% of all patients in nursing homes are affected,[14,15] as well as 34% of patients with spinal cord injuries and those in rehabilitation units.[16,17]

An estimated 15% of all patients with diabetes develop foot ulcers.[18]These often result from painless trauma (i.e., pressure) when patients wear ill-fitting shoes and socks, step on sharp objects, or stub their toes. One of the more serious complications of diabetes is peripheral neuropathy. Diabetic peripheral neuropathy has several effects in the lower extremity. First, autonomic dysfunction and associated denervation of dermal structures cause decreased sweating, dryness, and thus loss of integrity of intact skin, which provides an ideal site for microbial invasion.[19] Second, somatic neuropathy results in sensory loss in the affected area, which makes it difficult for patients to notice or feel an ulcer. In such cases, the patient may not seek treatment until after the wound progresses and becomes infected. Third, a combination of sensory and motor dysfunction can cause the patient to place abnormal stress on the foot, which produces trauma and predisposes to infection. In other words, the neuropathic foot does not ulcerate spontaneously; the combination of some form of trauma and neuropathy generates an ulcer. The most common causal pathway to diabetic foot ulceration has been identified as the combination of neuropathy (sensory loss), deformity (e.g., prominent metatarsal heads), and trauma (e.g., ill-fitting footwear).[20] For patients with diabetes who have peripheral neuropathy, the annual incidence of first foot ulcers is as high as 7.2%.[21] Therefore, close monitoring and immediate intervention are necessary to avoid high morbidity and mortality associated with diabetic foot and pressure ulcers.[22]

COMPLICATIONS IN PATIENTS WITH CHRONIC WOUNDS

Among 16 million patients with diabetes (diagnosed and undiagnosed) in the United States, an estimated 1575 lower-extremity amputations are performed each week (82,000 each year),[23] 84% of which are preceded by a foot ulcer.[24] Limb amputation in patients with diabetes is associated with an increased risk of further amputation in the same

Table 1. Morbidities Associated with Diabetic Foot and Pressure Ulcers

1	Cellulitis
2	Local infection/abscess
3	Osteomyelitis
4	Secondary infection (pneumonia, urinary tract infection, endocarditis, etc.)
5	Sepsis
6	Necrotizing fasciitis
7	Amputations (heel ulcers)
8	Pain
9	Loss of ability to ambulate
10	Depression
11	Death

Table 2. Actions/Events with Associated Costs Related to Treatment and Management of Diabetic Foot and Pressure Ulcers

1	Wound dressings
2	Management of bacterial colonization and infection (e.g., wound or blood cultures, antibiotics, debridement)
3	Care by health professionals
4	Radiology
5	Therapeutic procedures
6	Medications (analgesics, antibiotics)
7	Prosthesis
8	Gait training and maintenance after prosthesis
9	Death
10	Lawyer fees

patients, and has a five-year mortality rate of 39% to 68%.[25] Patients with diabetes admitted to a nursing home with a pressure ulcer were observed to have an 88.1% greater mortality rate ($p<0.001$) within one year than those without diabetes with similar foot wound infections.[14] These patients also are at risk for amputation, which has a five-year mortality rate in excess of 40%.[26] Amputation secondary to a foot ulcer is high in patients with both Type 1 and Type 2 diabetes. The mortality rate of patients with diabetes who undergo amputation is as high as 50% at four years.[27]

Sepsis, a major contributor to the high rates of morbidity and mortality, often originates in a pressure or diabetic foot ulcer, which acts as a portal of entry for infection. As patients with diabetes frequently have impaired immune function (in addition to ischemia and neuropathy), they are predisposed to infection.[28,29] A wound with high concentrations of bacteria (e.g., *Streptococcus* group B, *Pseudomonas aeruginosa*, *Enterococcus*, and others) remains a source of sepsis even in the absence of clinical infection. Furthermore, infections associated with diabetic ulcers are generally more severe and more difficult to treat than similar foot-wound infections in patients without diabetes. It also has been demonstrated that as the wound progresses in grade and stage, the prevalence of diabetes-related amputations increases significantly.[30]

One of the reasons for an increased infection rate in patients with diabetes is that hyperglycemia may cause the virulence of microorganisms to increase. For example, *Candida albicans* expresses a surface protein that has close homology with the C3b receptor.[31,32] In the hyperglycemic state, expression of the surface protein is enhanced so that the microorganism binds competitively to the C3b receptor and inhibits opsonization of the microorganism and subsequent phagocytosis.[33] Further, patients with diabetes have dysfunction of the macrophage system, which results in increased susceptibility to infection and delayed wound healing. Experimentally, macrophages in the presence of diabetes have demonstrated a reduction in the release of essential cytokines (TNF-α and IL-1β),[34,35] and reduced phagocytic activity.[36]

COSTS AND QUALITY OF LIFE

Not only are diabetic foot and pressure ulcers a source of extreme suffering, they also are extraordinarily expensive, both for the patient and the hospital, particularly if they remain unhealed. Costs of treating the associated complications in a single hospital stay from a pressure ulcer often exceed $200,000 per patient (this occurs in select cases in which the ulcer is not recognized initially and complications from the wound develop).[37] The two-year cost for a diabetic foot ulcer in a patient between 40 and 65 years old has been calculated at an average of $27,987.[38] This figure only accounts for direct medical costs and excludes costs of continued care or amputation. Amputation costs are as high as $60,000 per patient per year.[39] None of these estimates takes into account the effect of these ulcers on the personal, social, and economic aspects of the life of patients and their families.

Pressure ulcers and diabetic foot ulcers have a profound impact on patients' quality of life in terms of their functionality and well-being, including feelings of anxiety and depression, as well as loss of mobility and independence. The requirement for time away from work jeopardizes job prospects and is a cause of anxiety for the patient.

PREVENTION

Prevention of chronic ulcers is the ideal scenario. Currently, no definitive paradigm is available for effective continuous and proven prevention of pressure ulcers. Standards of care, including maximum pressure relief and turning of patients every 2 to 3 hours, do not assure prevention of these ulcers. We emphasize that turning and pressure relief are absolute minimum standards of care for any bed-bound or immobilized patient.

Patients at high risk for developing diabetic foot problems are advised to practice preventive foot self-care, and often are prescribed special shoes to protect their feet from trauma. When patients have lost or reduced sensation in their feet, however, the normal perception of pain is no longer present to prompt them to check their feet or ask others to do so. In this case, other aspects of illness representation (e.g., patients' beliefs about causes, their perceptions of their own ability to halt progression) must be relied upon to direct their behavior. Furthermore, it must be emphasized that new ulcers usually appear as a superficial lesion on the skin and, if recognized immediately, often can be treated successfully with negligible side effects. Osteomyelitis, pain, infection, amputation, and mortality can be avoided by early recognition and treatment. By modifying risk factors and improving foot care among patients with diabetes, an estimated 50% of lower-extremity amputations could be prevented.[40]

Two common misconceptions—chronic ulcers can develop only when circulation is poor and development of a foot lesion is always accompanied by pain—have no scientific basis. Correct understanding of the causes of foot problems and concern regarding the possibility of amputation are the strongest predictors of good foot care.[41]

SUCCESSFUL TREATMENT OF DIABETIC FOOT AND PRESSURE ULCERS

The grave consequences of diabetic ulcers make it necessary to determine the best combination of therapies to prevent progression. The authors' clinical experience demonstrates that these patients can be treated successfully, and their wounds healed completely, if an integrated treatment protocol is implemented. The methods presented in this article are applicable to both inpatients and outpatients. Optimal treatments for pressure and diabetic foot ulcers are similar. Chronologically, they are:

1. Recognition that all patients with diabetes or limited mobility are at risk for a sacral, ischial, trochanteric, or heel pressure ulcer.
2. Daily examination of the skin on the heels, feet, pelvis, and sacrum in bed-bound patients and those with diabetes.
3. Initiation of a treatment protocol immediately upon recognition of a break in the skin; i.e., emergence of a new wound. All underlying medical conditions must be treated by the primary care physician, who needs to maintain continuous communication with the patient and other clinicians taking care of the patient.
4. Objective measurement of every wound (at a minimum, weekly), which currently requires digital photography and planimetry, and thorough documentation of its progress.
5. Establishment of a moist wound-healing environment.
6. Relief of pressure from the wound.
7. Debridement of all non-viable tissue in the wound.
8. Elimination of all drainage and cellulitis.
9. Consideration of biological therapies for patients with wounds that do not heal rapidly after initial treatment.
10. Continuous physical and psychosocial support for all patients.

EARLY INTERVENTION AND COMPREHENSIVE TREATMENT

Little doubt exists that if one were to locate ulcers in all afflicted bed-bound patients, and begin treatment immediately, the incidence of Stage IV ulcers (full-thickness skin loss with tissue necrosis, or damage to bone, muscle, or supporting structures)[42] would be decreased dramatically, if not eradicated completely.

Recognition that a chronic wound has an underlying physiological impairment to healing is essential in designing a treatment plan. Initial recognition of a diabetic foot ulcer should prompt an immediate visit with the patient's physician, podiatrist, or surgeon. The possibility for vascular intervention must be assessed in all patients with lower extremity ulcers who have impaired arterial inflow. Additionally, when infection is controlled by debridement and other appropriate therapy, biological therapy is one option that may be used to accelerate contraction of these wounds. The relationship between early intervention and prevention of amputation has been well documented.[43-45] All patients with diabetes and those at risk for localized pressure (i.e., spinal-cord injured and bed-bound patients) should be examined daily. Any new wound (i.e., any break in the skin) requires mandatory intervention.

In addition to early recognition and intervention, comprehensive therapy is vital to successful treatment. As soon as an ulcer is recognized, immediate comprehensive treatment should be initiated with the clinical endpoint of healing, unless other mitigating factors (e.g., palliative care) are documented in the patient's chart. The healthcare provider(s) responsible for treating the wound should have a choice of interventions that includes the entire range of all available therapies.

No patient with any chronic wound should be advised to remain in bed. If a patient is on a respirator or otherwise bed-bound, physical therapy should be initiated. This approach not only helps accelerate wound closure, but also decreases the co-morbidities associated with bed-bound patients (e.g., pneumonia, new additional ulcers, and deep vein thrombosis).

OBJECTIVE MEASUREMENT

Only recently have healing rates been established for pressure and diabetic foot ulcers, thus providing a template against which to gauge the effectiveness of a given treatment. At least once a week, length, width, and depth of the wound must be measured in all patients as a mandatory part of the protocol regimen. Planimetry is optimal, and a Q-tip may be used to assess depth, measuring it against a simple ruler. The ambiguous, but commonly used phrase that a wound "looks good" should be eliminated. All patients have agreed that short of a healed wound, there is no such thing as a "good-looking" wound.

WOUND-BED PREPARATION

The goal of wound-bed preparation is to attain well-vascularized granulation

tissue without any signs of local infection, which include drainage, cellulitis, and odor. Removal of scar tissue also is essential. Proper debridement prepares the wound bed and stimulates the healing process simultaneously. Maximal wound-bed preparation includes stimulation of granulation tissue (new collagen and angiogenesis) and reduction of bacteria in the wound. Adequate wound-bed preparation results in decreased morbidity and improved healing.

In preparation of the wound bed, it is important to direct each local or topical therapy toward creating a moist wound-healing environment while facilitating the formation of granulation tissue and treating the underlying disease. Thus, after debridement of an infected wound, topical antibiotics may be efficacious. In such cases, silver sulfadiazine cream provides broad-spectrum antibacterial coverage, while newer forms of continuous release provide a slower release of silver ions. Currently, many forms of the biologically active silver cation exist that can provide a more sustained release of silver to the wound and, thus, to antimicrobial activity. Cadexomer Iodine® (Healthpoint in the U.S., Smith & Nephew in the U.K) is another alternative that can be used to remove the bacterial burden and exudates.

Collagenase (Smith & Nephew) is prescribed commonly as a topical agent for chemical debridement. Collagenase is an endogenous protein demonstrated experimentally to maintain a role in formation of new blood vessels and aid in healing, specifically wound contraction and closure. It also may prevent fibrous necrosis from recurring while stimulating well-vascularized granulation tissue and wound closure.

RELIEF OF PRESSURE

Pelvic pressure ulcers, heel ulcers, and diabetic foot ulcers are caused, in part, by pressure. However, the term "pressure ulcer" is a partial misnomer because it is not only pressure, but rather a combination of factors that cause ulcers, including decreased blood flow. The following four criteria are the minimum prerequisites that must be addressed to achieve healing: 1) early recognition of the wound; 2) adequate arterial inflow to the affected area (e.g., if the wound is in the limb); 3) removal of pressure from the ulcer and adjacent areas; and 4) successful eradication of infection.

In clinical practice, most diabetic foot ulcers and many pressure ulcers fail to heal because relief of pressure from the ulcer is not implemented. Crucial to remember is that sensory loss, which occurs in diabetic neuropathy, permits pressure of any magnitude to be applied to the ulcer without the pain or discomfort experienced by those with normal sensation. Therefore, it is of critical importance to ensure pressure is relieved from all wounds, but in particular, diabetic foot ulcers[46-49] and pressure ulcers.

For diabetic foot and pressure ulcers, offloading remains the absolute minimum standard of treatment for relieving pressure. The most studied and effective offloading technique for treatment of neuropathic wounds, especially those of the midfoot, is total contact casting, or TCC. It is considered the gold standard for offloading.[46] A TCC is minimally padded and carefully molded to the shape of the foot. These special casts redistribute weight off the ulcer site and allow patients to walk while the ulcer heals. Also available is an "instant" TCC, which is generally more available and easier to apply, because the fabrication of a TCC requires considerable expertise, and can be both time-consuming and expensive.[47] Alternatives to total contact casting include removable casts, such as the Scotch cast boot,[48] the air cast boot, a half shoe, and a polystyrene "foam" leg trough.[49]

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

ALTERNATING AIR THERAPY FOR PELVIC AND SACRAL PRESSURE ULCERS

Alternating air therapy (Pegasus Renaissance®, Arjo Pegasus, Inc., USA & Pegasus Ltd, UK) has been demonstrated to increase blood flow in the sacral area significantly, while it decreases pressure.[45,50] The alternating air mattress is designed to relieve pressure in the desired area and avoid pressure damage rapidly and completely. This state of near zero pressure is accomplished by using 3-cell cycle technology, composed of the alternation of air in an inflated cell next to a partially inflated cell, next to a completely deflated cell. This 3-cell cycle technology increases blood flow to the otherwise compressed body parts, without changing body temperature. The 3-cell cycle model is more effective and more cost effective than static or alternative dynamic support surfaces. Pressure ulcers can be healed successfully even in the most critically ill patients if the paradigm outlined in this report is followed.

MECHANICAL DEBRIDEMENT

Debridement is performed to stimulate healing and accelerate contraction, and is a mandatory part of the clinician's protocol regimen. Several methods of debridement are used. Small ulcers may be debrided at the bedside, whereas more extensive ulcers are debrided in the operating room. Debriding any wound to the level in which scar, non-viable tissue, and infection are no longer present—even if down to the bone—has proven to be safe and therapeutic. In contrast, only minimal viable tissue should be excised. The wound margins should not be extended more than 1 mm or 2 mm. Currently, topical fibrin glue is used frequently to prevent blood loss and facilitate debridement.

ELIMINATION OF ALL DRAINAGE AND CELLULITIS

Cellulitis occurs when infection from the ulcer spreads to surrounding tissue. This is a serious and frequent complication in diabetic foot and pressure ulcers that is typically not treated effectively. All cellulitis must be eliminated with the use of antibiotics and surgical debridement. Drainage also must be eliminated, because it is a sign of infection. A wound healing successfully is one that has no cellulitis or drainage.

BIOLOGICAL THERAPIES

Biological therapies include growth factors and cell therapies. The term, skin equivalent, is often misused as in practicality it means that cells and the subsequent release of their growth factors are being administered to the wounds, but not a skin equivalent, which is a completely different alternative to healing a chronic wound. Cell therapy[50-66] adds cells and growth factors to an environment deficient in cells and/or growth factors. Both cell layers are grown from infant foreskin. Bilayered HSE (Figs. 1-4)

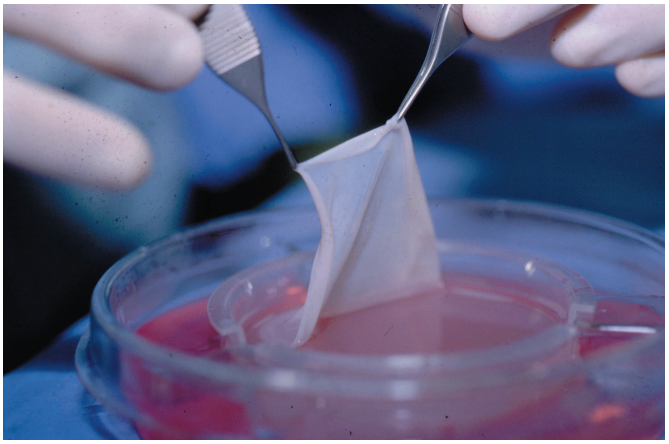

Figure 1. Saline being applied in Petri dish such that bilayered living human skin equivalent (HSE) can be removed easily from its culture medium. It is being lifted with two smooth forceps. Bottom layer is the fibroblast side, and top layer is the keratinocyte layer.

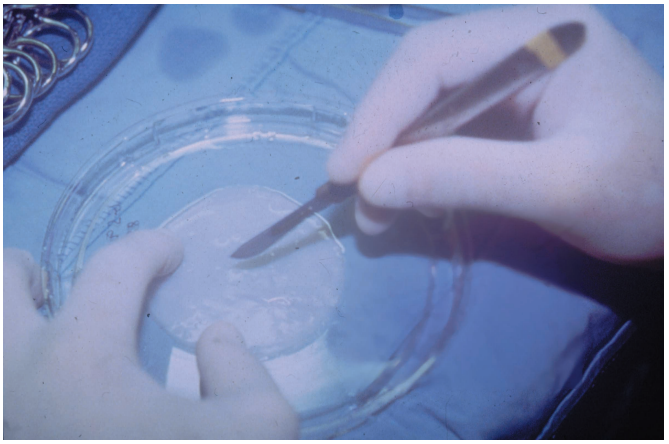

Figure 2. Bilayered human skin equivalent (HSE) on top part of sterile Petri dish in which it is packaged, before making of slits with a #10 blade.

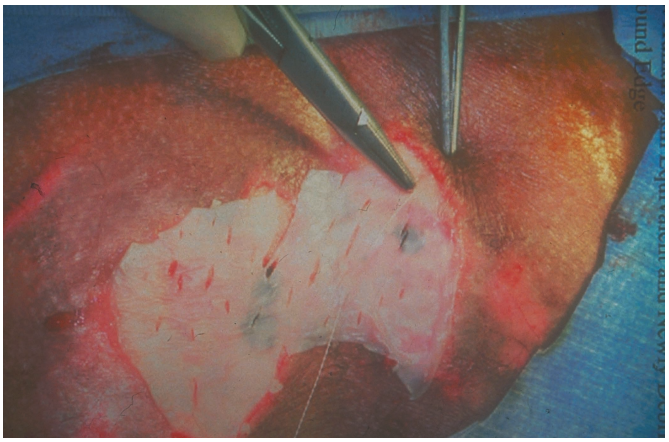

Figure 3. Note bilayered human skin equivalent (HSE) being trimmed so there is a 1-mm distance between freshly cut skin edge of cell therapy and freshly debrided skin edge. This small gap ensures when pressure ulcer is freshly debrided, freshly cut bilayered HSE will release cells to stimulate healing. The goal after application of bilayered HSE is to have fibroblasts in contact with well-vascularized wound.

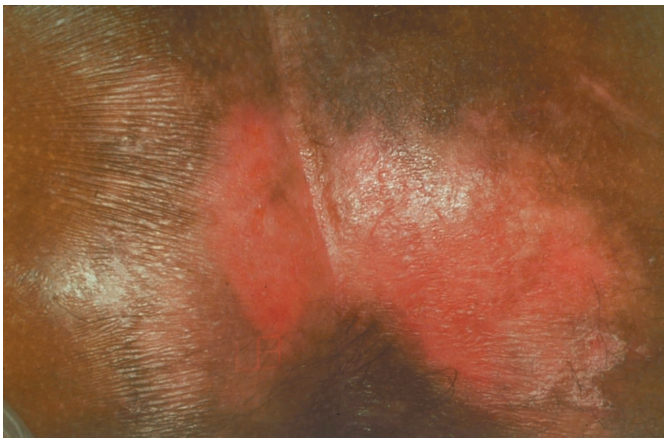

Figure 4. One month after an application of bilayered human skin equivalent (HSE), pressure ulcer has healed completely.

—FDA approved for the accelerated closure of multiple types of chronic wounds; i.e., including diabetic foot ulcers—looks and feels like human skin, but its biological activity is distinct from that of an autologous skin graft in that it is a potent stimulator of wound healing. A single application of bilayered living HSE early in the course of ulcer formation, specifically in patients with diabetes and those with superficial pressure ulcers, could prevent progression of these wounds as well as accelerate their closure. Acceleration of closure decreases risk of infection.

Bilayered living HSE is placed after complete hemostasis is attained. Adaptic® (Johnson & Johnson, New Brunswick, New Jersey, USA) is then placed over the HSE, followed by Vaseline® (Chesebrough-Ponds, Greenwich, Connecticut, USA) gauze wrapped around sterile cotton, followed by Tegaderm™ (3M Health Care, St. Paul, Minnesota, USA). This procedure can be performed easily on an outpatient, inpatient, or a patient in a nursing home (see Figs. 1-4).

Another available therapeutic aid is a dermal equivalent (Smith & Nephew). It is different from the bilayered living HSE in that it has fibroblasts but no keratinocytes.[63,64] It is FDA approved for treatment of diabetic foot ulcers.[65,66] This agent is most successful if applied weekly.

If proper wound-bed preparation does not result promptly in accelerated closure, consideration should be given to treatment with bilayered living HSE, which has been shown to produce rapid closure. High success rates in the healing of chronic wounds (>85% for diabetic foot ulcers, and 80% for pressure ulcers, before progression to Stage IV) can be attributed largely to the potent biological activities of cell therapies;[45,55] the subsequent synthesis and release of growth factors from the cells; and proper wound-bed preparation, which includes debridement, treatment of infection, and pressure offloading.

CONCLUSION

The intent of this article is to establish clear guidelines for a standard of care that ensures patients receive optimal

treatment for their diabetic foot ulcers and pressure ulcers. This standard of care includes: 1) recognition that all bed-bound patients and patients with diabetes are at risk for developing ulcers; 2) daily examination of all at-risk areas, which include feet, sacrum, heels, as well as ischial and trochanteric areas; 3) initiation of a comprehensive treatment protocol immediately upon emergence of a new wound; 4) objective measurement of all wounds; 5) establishment of a moist wound-healing environment; 6) pressure relief from the wound; 7) debridement of all non-viable tissue; 8) elimination of all drainage and cellulitis; 9) consideration of biological therapy for non-healing ulcers; and 10) continuous psychosocial support, nutritional consultation, and physical therapy. If these protocol guidelines are followed, most diabetic foot and pressure ulcers are expected to heal. Treatment for any patient with a pressure ulcer or diabetic foot ulcer must incorporate all aspects discussed in this treatment protocol to achieve rapid successful healing, as measured by wound contraction without any cellulitis or drainage. Early detection and treatment are crucial, and must remain the goal for bed-bound patients and those with diabetes.

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