Wound care: The role of advanced wound healing technologies

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Wound repair and regeneration is a highly complex combination of matrix destruction and reorganization. While major hurdles remain, advances over the past generation have improved the clinician’s armamentarium in the medical and surgical management of this problem. The purpose of this manuscript is to review the current literature regarding the pragmatic use of three of the most commonly employed advanced therapies; namely, bioengineered tissue, negative pressure wound therapy, and hyperbaric oxygen therapy with a focus on the near-term future of wound healing, including stem cell therapy. (J Vasc Surg 2010;52:595-665.)

Wound repair is an orchestra of highly integrated biological and molecular events of cell migration and proliferation, and of extracellular matrix deposition and remodeling. Certain pathophysiologic and metabolic conditions can alter this normal course of events so that healing is impaired or delayed, resulting in chronic, nonhealing wounds. Diabetic foot ulcers (DFUs) readily become chronic and the factors that delay wound healing are multiple and relate both to diabetes and to the effects of its complications. The costs associated with the healing of an ulcer have been noted to be as high as $45,000; however, these estimates do not include the deleterious effects on the patient’s quality of life because of impaired mobility and substantial loss of productivity. Clearly, the healing of ulcers in a timely manner is of central importance in any plan for amputation prevention and limb preservation. The integration of technological advances with our understanding of the complex cellular and biochemical mechanisms of wound healing has led to the development of various advanced wound healing modalities, such as bioengineered skin and tissue equivalents, negative pressure wound therapy (NPWT), and hyperbaric oxygen therapy. This article examines the latest advances in wound healing using these three therapeutic categories and assesses their implications for clinical practice.

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BIOENGINEERED SKIN AND DERMAL SUBSTITUTES OR EQUIVALENTS

Cell-based technologies to deliver exogenous growth factors to the wound bed. Autogenous and non-autogenous skin grafts, commonly used for the healing of skin ulcerations, may be associated with a number of limitations such as risks of immune rejection, infection transmission, and the creation of a donor site that is at risk of developing pain, scarring, infection, and/or delayed healing. The need for a readily available, non-antigenic tissue that possesses many of the histological and functional characteristics of normal human skin spawned the evolution of growing human tissues for transplantation. Tissue engineering has revolutionized skin grafting from the initial autograft and allograft preparations to biosynthetic and tissue-engineered skin replacements and cell-based therapies. These advanced therapies include cultured autologous keratinocyte grafts, cultured allogeneic keratinocyte grafts, autologous/allogeneic composites, acellular collagen matrices, and cellular matrices. A number of products are commercially available, and many others are in development. The ones that are currently available include human fibroblast-derived dermal substitute, human fibroblast-derived temporary skin substitute, and allogeneic bi-layered cultured skin equivalent.

Human fibroblast-derived dermal substitute. Human fibroblast-derived dermal substitute (Dermagraft, Advanced Biohealing Ltd, La Jolla, Calif) is composed of fibroblasts, extracellular matrix, and a bioabsorbable scaffold (Fig 1). It is produced by culturing human dermal fibroblast cells derived from newborn foreskin tissue onto a bioabsorbable polyglactin mesh scaffold. As the fibroblasts proliferate to fill the interstices of this scaffold, they secrete human dermal collagen, matrix proteins, growth factors, glycosaminoglycans, and cytokines to generate a three-dimensional, allogeneic, human dermal substitute containing metabolically active, living cells with a preferred, nearly parallel alignment of the collagen fibers within human dermal substitute. The critical dependence of the therapeutic properties of this living dermal implant on the recovery of protein synthesis, growth factor expression, and

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angiogenesis has been demonstrated. Unlike human skin, human fibroblast-derived dermal substitute does not contain macrophages, lymphocytes, blood vessels, or hair follicles. Human fibroblast-derived dermal substitute has good resistance to tearing and is packaged with bovine serum and a saline-based cryoprotectant that contains 10% dimethyl sulfoxide (DMSO). Cryopreservation helps maintain cell viability and provides off-the-shelf availability. However, because the packing medium may also contain traces of bovine serum, human fibroblast-derived dermal substitute is contraindicated in patients with known hypersensitivity to bovine products. Human fibroblast-derived dermal substitute is also contraindicated for use in ulcers that have signs of clinical infection or in ulcers with sinus tracts.

Laboratory studies suggest this bio-engineered dermal substitute promotes the healing of chronic ulcerations via two principal modes of action. First, it provides living, human dermal fibroblasts that deposit matrix proteins and facilitate angiogenesis. It also provides a preformed collagen matrix, receptors, and bound growth factors that facilitate the migration and colonization of the host’s epithelial cells, which promote wound closure. Previous studies have shown human fibroblast-derived dermal substitute to be most effective in treating ulcers of greater than 6 weeks duration. It may be possible that chronic ulcers are deficient in many of the factors necessary for healing and are most likely to benefit from human fibroblast-derived dermal substitute treatment.

Human fibroblast-derived dermal substitute is designed to assist in restoration of the dermal bed in an ulcer to improve the wound healing process and allow the patient’s own epithelial cells to migrate and close the wound. It is approved by the United States Food and Drug Administration for the treatment of full-thickness, chronic (>6 weeks) diabetic foot ulcers extending through the dermis, but not involving tendon, muscle, joint capsule, or bone.

The efficacy of human fibroblast-derived dermal substitute in the healing of full thickness chronic diabetic wounds has been confirmed in many studies. A randomized, controlled, multicenter trial evaluated 314 patients with chronic diabetic foot ulcers for complete wound closure by 12 weeks and found that 30.0% (39/130) of human fibroblast-derived dermal substitute patients healed compared with 18.3% (21/115) of control, wet-to-dry dressing patients ($P = .023$). In addition, the group of patients who received human fibroblast-derived dermal substitute experienced significantly fewer ulcer-related adverse events. Another prospective, multicenter, randomized controlled 12-week study that enrolled 28 patients with chronic diabetic ulcers found significantly more patients in the human fibroblast-derived dermal substitute group achieved wound closure significantly faster than the control group ($P = .004$); the study group also exhibited a statistically significant higher percent of wound closure by week 12 as compared with patients in the control arm ($P = .002$). Interestingly, the percentage of patients who experienced an infection involving their study wound was lower in the human fibroblast-derived dermis group than in the control group.

One potential problem that can arise from the application of a human dermal substitute onto an allogeneic host is the initiation of an immune response leading to its rejection. Human fibroblast-derived dermis has passed extensive safety testing, and to date, there has been no reported case of rejection in clinical use. This may be secondary to the inherent properties of human dermal substitute since it is derived from neonatal human tissue that has undeveloped human leukocyte antigen tissue markers. In addition, dermal-derived fibroblasts are relatively non-antigenic, do not express human leukocyte antigen-DR markers, and are therefore, not expected to cause an immune reaction.

**Risk factors related to improved healing with human fibroblast-derived dermal substitute.** Data from a Phase III randomized trial were analyzed to find risk factors related to ulcer healing. Of interest, age, race, diabetes type, ulcer duration prior to enrollment, and hours of weight-bearing were not associated with healing rate. Initial ulcer area, gender, a history of ulcer infection, and change in hemoglobin A1c (Hgb A1c) were associated with altered healing rates.

An initial ulcer area greater than 2 cm$^2$ was associated with a 1.5 times greater incidence of wound closure ($P = .02$). Females were 2.0 times more likely to heal than males ($P = .009$). An episode of infection during the 12 weeks of treatment was associated with a 3.4 times increased risk of non-closure ($P < .01$).

In another study, Browne et al reported on the importance of controlling bacterial load prior to the use of human fibroblast-derived dermal substitute. The authors found an association between the bacterial load and healing rate both before and after human fibroblast-derived dermal substitute application. They recommended treatment of patients...
with combination antibiotics until the bacterial burden was reduced to less than 10^6 colony forming units/gram prior to the application of living skin substitutes or growth factors. The initial and terminal Hgb A1c levels did not independently relate to wound closure. To better determine the relationship between glucose control and wound healing, Marston and colleagues calculated the change in Hgb A1c between initial and 12-week levels. Patients with a decrease in this value were expected to have better glucose control on average than those with an increasing level. In the control group, there was no significant difference in the rate of healing in those with improving compared with worsening Hgb A1c. Further, the number healed in the human fibroblast-derived dermal substitute treated group with worsening Hgb A1c was similar to the control rates (20.2%). However, the number of subjects that healed in the human fibroblast-derived dermal substitute group with an improving Hgb A1c (46.7%) was significantly higher than in the other three groups (P = .008). These data are detailed in Fig 2. Allen et al assessed the cost-effectiveness of human fibroblast-derived dermis in the treatment of the diabetic foot ulcer compared with standard treatment. The authors developed a Markov model to simulate, over a 52-week period, the health status of a cohort of 100 patients with a diabetic foot ulcer treated either with conventional therapy or with human fibroblast-derived dermis. They concluded that because human fibroblast-derived dermis heals more ulcers within 52 weeks, the average cost per healed ulcer is lower (53,522 French francs [FF] vs 56,687 FF for standard treatment). The incremental cost-effectiveness of human fibroblast-derived dermis equals 38,784 FF, indicating the extra investment that the decision-maker has to accept for an additional ulcer healed with human fibroblast-derived dermis compared with conventional treatment.

**Allogeneic bi-layered cultured skin equivalent.** Allogeneic bi-layered cultured skin equivalent (Apligraf; Organogenesis Inc, Canton, Mass) is a living, biological dressing developed from neonatal foreskin and consists of living cells and structural proteins. Like human skin, this allogeneic bi-layered cultured skin equivalent has both an upper epidermal and a lower dermal layer and contains human skin cells. The lower dermal lattice combines bovine type 1 collagen and cultured human neonatal dermal fibroblasts, which produce additional matrix proteins and organize the provided structural proteins. The upper epidermal layer is formed by promoting human epidermal keratinocytes to first multiply and then to differentiate to replicate the architecture of the human epidermis and act as a barrier to prevent water loss and infection. Allogeneic bi-layered cultured skin equivalent has been shown to produce all cytokines and growth factors that are produced by the normal skin during the healing process. Unlike human skin, allogeneic bi-layered cultured skin equivalent does not contain melanocytes, Langerhans’ cells, macrophages, lymphocytes, or other structures such as blood vessels, hair follicles, or sweat glands.

Although the precise mode of action is not clear, allogeneic bi-layered cultured skin equivalent has been quoted to behave similarly to a partial thickness autograft in that it provides immediate wound coverage and interacts with adjacent tissue after implantation. Similarities between dermal layers of the host and graft may facilitate the cross-over activity of mediators and response to signals from both the host and graft dermal cells. Allogeneic bi-layered cultured skin equivalent has also been noted to act through at least three modes of healing: secondary intention, persistent wound closure with underlying healing, and frank graft take. It is believed that the allogeneic bi-layered cultured skin equivalent acts by both filling in the wound with extracellular matrix and by inducing the expression and production of numerous growth factors and mediators such as interleukin transforming growth factors (TGF-β), granulocyte-macrophage colony-stimulating factor, platelet-derived growth factor, and cytokines that contribute to wound healing by the stimulation of wound contraction and epithelization. A study investigating the effects of dermal replacement therapy on blood flow at the base of diabetic foot ulcers noted that blood flow increased by an average of 72% in the base of five of the seven ulcers studied. The changes in blood flow observed may reflect angiogenesis in the newly formed granulation tissue and/or vasodilatation of existing vessels, processes that are possibly enhanced by the allogeneic bi-layered cultured skin equivalent application.

Allogeneic bi-layered cultured skin equivalent is packaged in a sealed heavy-gauge polyethylene bag with a 10% CO2/air atmosphere and an agarose nutrient medium. It is contraindicated in patients with known allergies to bovine collagen or hypersensitivity to the components of the shipping medium. One of the previous inconveniences with allogeneic bi-layered cultured skin equivalent was its need to be shipped overnight based on date of patient application. The newly improved shipping box with better insulation and temperature maintenance now affords allogeneic bi-layered cultured skin equivalent a 10-day shelf life and the clinician some flexibility on the date of application. Antiseptic agents such as Dakin’s solution, mafenide acetate, scarlet red dressing, tincoban, zinc sulfate, povidone-iodine solution, and chlorhexidine have been determined...
to be cytotoxic to allogeneic bi-layered cultured skin equivalent and should not be used immediately prior to its application.

Apligraf is the first bi-layered living skin equivalent approved in the United States for the treatment of chronic venous and full-thickness neuropathic diabetic foot ulcers of greater than three weeks’ duration that extend through the dermis but without tendon, muscle, capsule, or bone exposure.21

In a large, multicenter, randomized, prospective clinical trial, allogeneic bi-layered cultured skin equivalent was shown to heal non-infected, non-ischemic chronic plantar diabetic foot ulcers faster and in more patients than conventional therapy.5 By 12 weeks of treatment, 56% (63/112) of chronic diabetic foot ulcers treated with allogeneic bi-layered cultured skin equivalent were 100% closed, compared with 39% (36/96) of ulcers treated with conventional therapy (debridement plus saline dressings alone and total off-loading \( P = .0026 \)).5 The median time to wound closure was 65 days for diabetic foot ulcers treated with allogeneic bi-layered cultured skin equivalent versus 90 days for ulcers treated with conventional therapy \( (P = .0026) \). A similar study conducted in the European Union and Australia reported comparable results.22 The incidence of adverse reactions was similar between the two groups, with the exception of osteomyelitis and lower-limb amputations, both of which were noted to be less frequent in the allogeneic bi-layered cultured skin equivalent group.5,23 Allogeneic bi-layered cultured skin equivalent is well-tolerated, appears to be immunologically inert, with no clinical evidence of rejection by any patient.18,24

Because the allogeneic bi-layered cultured skin is made up of viable human cells, it cannot be terminally sterilized.25 Safety concerns, which have been addressed, include the risk of possible transmission of infection, immunogenicity, immunological graft rejection, and tumor formation.25 The maternal blood of the neonatal donor and the working cell banks are thoroughly screened for infectious agents, pathogens, and other contaminants.25

Allogeneic bi-layered cultured skin equivalents are of considerable cost and should therefore be reserved for chronic foot ulcers that have failed to respond to the currently available standard care.26 Redekop et al found that treatment with allogeneic bi-layered cultured skin equivalent plus good wound care resulted in a 12% reduction in costs over the first year of treatment compared with good wound care alone.27 This benefit was realized after 5 months, the crossover point of the two cost curves. Allogeneic bi-layered cultured skin equivalent use increased the amount of ulcer-free time by 1.53 months (7.78 vs 6.25), reduced the risk of amputation (6.3% vs 17.1%),27 and subsequently was cost-effective in the long-term. Langer and Rogowski assessed the cost-effectiveness of growth factors and tissue-engineered artificial skin for treating chronic wounds based on a review of 11 qualifying economic evaluations.28 The authors noted that, although some growth factors and tissue-engineered artificial skin products had favorable cost-effectiveness ratios in selected patient groups with chronic wounds, health care providers and coverage decision makers should take not only the high cost of the biotechnology product but the total cost of care into account when deciding about the appropriate allocation of their financial resources.28

**Negative pressure wound therapy.** Since its introduction in the United States in 1997, negative pressure wound therapy (NPWT) or vacuum-assisted closure has emerged as a commonly employed option in the treatment of complex wounds (Fig 3). The incorporation of NPWT into wound treatment regimens has been advocated by many clinicians, and NPWT has been noted to help decrease the number of dressing changes, reduce the time between debridement and definitive closure, and reduce costs associated with a protracted course of hospital stay.29,30

Armstrong and colleagues evaluated the efficacy of NPWT to heal 31 indolent diabetic foot wounds immediately after wide surgical debridement. A cessation of therapy protocol was utilized where NPWT was discontinued when the wound bed approached 100% coverage with granulation tissue and no exposed tendon, joint capsule, or bone. They noted that 90.3% of the wounds treated with NPWT healed at the level of debridement without the need for further bony resection in a mean 8.1 \( + 5.5 \) weeks.30 In a randomized trial, Eginton et al compared the wound healing efficacy of NPWT and conventional moist dressings to treat large diabetic foot ulcers, and found NPWT decreased wound volume and depth significantly more than...
moist gauze dressings (59% vs 0% and 49% vs 8%, respectively). 31

Recently published trials have further demonstrated the wound-healing efficacy of NPWT. Blume and coworkers compared the safety and clinical efficacy of NPWT with advanced moist wound therapy (AMWT) to treat diabetic foot ulcers in a multicenter, randomized, controlled trial. They enrolled 542 subjects, 79% male, with a mean age of 58 years, who were randomized to receive either NPWT or AMWT and standard off-loading therapy as needed. 32 The authors noted that a greater proportion of foot ulcers achieved complete ulcer closure with NPWT (73/169; 43.2%) than AMWT (48/166; 28.9%) within the 112-day active treatment phase (P = .007). The Kaplan-Meier median estimate for 100% ulcer closure was 96 days (95% confidence interval: 75.0, 114.0) for NPWT and not determinable for AMWT (P = .001). The authors noted no significant difference between the groups in treatment-related complications at 6 months.

Similarly, a 16-week, 18-center, randomized clinical trial conducted by Armstrong and Lavery, involving 162 diabetic patients with larger and more complex wounds than those from previous randomized trials, found that NPWT healed more wounds after partial foot amputation versus the standard of care (43 [56%] vs 33 [39%; P = .040). The authors noted that NPWT produced faster wound-healing rates (P = .005) and faster granulation tissue formation rates, versus standard of care, based on the time needed to complete closure (P = .002). 33 Resource utilization for patients treated with NPWT also was evaluated in this same study population. Apelqvist 34 and coworkers reported that patients randomized to the NPWT group required fewer surgical procedures (including debridement) than the control group (43 vs 120; P < .001), fewer average number of dressing changes (41 [range, 6-140] for NPWT versus 118.0 [range, 12-226] for control MWT [P < .0001]), and fewer outpatient treatment visits (4 [range, 0-47] in the NPWT versus 11 [range, 0-106] for control, [P < .05]). This yielded a cost savings in excess of $12,800 compared with standard therapy. Combined with the clinical data, these analyses provide compelling evidence that appropriate use of NPWT is efficacious and cost-effective in achieving healing of properly selected wounds, both on an inpatient and outpatient basis.

**Hyperbaric oxygen therapy.** Hyperbaric oxygen (HBO) has long been considered as a potential treatment modality for complicated or recalcitrant ulcers. Oxygen has been reported to stimulate angiogenesis, enhance fibroblast and leukocyte function, and normalize cutaneous microvascular reflexes. 35,36 Clinically, HBO has been demonstrated to improve transcutaneous pO2 in the limbs of some patients with ischemic ulcers. Significant side effects of treatment are uncommon, but may be severe, including barotraumatic otitis, hyperoxic seizures, and pneumothorax.

For the treatment of DFU, one randomized study was particularly influential in supporting use of HBO for complex wounds. Abidia and colleagues randomly assigned 18 patients with ischemic non-healing diabetic limb ulcers to 100% oxygen or air at 2.4 atmospheres for 90 minutes in a hyperbaric chamber daily. 37 In this double-blind study, oxygen and control groups received 30 sessions after which the outcome was measured. In the oxygen group, five of eight ulcers were closed completely, compared to one of the eight control ulcers (P = .27).

In another prospective study of diabetic foot ulcers, Kalani et al enrolled 38 patients with non-healing foot ulcers and basal transcutaneous oxygen levels in the foot below 40 mm Hg. 38 Seventeen patients were treated with HBO for 40 to 60 sessions, and 21 were treated with standard diabetic ulcer care. Patients were followed for 3 years. At final follow-up, 76% of patients treated with HBO had healed their DFU, and only 12% required limb amputation. In the standard care group, 48% had healed their foot ulcer at 3 years, and 33% required limb amputation.

In 2004, the Cochrane Collaborative reviewed hyperbaric oxygen therapy for chronic wounds and concluded that HBO reduces the risk of amputation for patients with DFU and increases the chance of healing at 1 year. 39 However, it was noted that these recommendations were based on small, underpowered studies and that further randomized studies were greatly needed to clarify the benefits of this costly therapy. Addressing some of the methodologic concerns of previous studies, a rather robust double-blind randomized controlled study conducted by Londahl and coworkers 40 suggested improved healing in the active HBO group compared with placebo at 1 year in patients suffering from complex diabetic foot wounds (52% vs 29%; P = .03). This study used an intent-to-treat analysis for patients with chronic (>3 month duration) neuropathic and neuroischemic wounds. All received treatment in a multiplace chamber receiving either active HBO or placebo (compressed air).

Further work has been conducted to identify better decision-making parameters for the use of HBO. Works have focused on the use of transcutaneous oxygen tension (TcPO2) as a predictive modality in selecting patients for HBO treatment. Specifically, Grolman et al measured TcPO2 in the ischemic limb of 36 patients breathing room air, followed by 100% O2. They found an increase of TcPO2 in the ischemic foot of >10 torr was associated with a healing rate of 70%, compared with a healing rate of 11% in those with an increase of <10 torr. 41 In a larger study of ischemic and non-ischemic DFUs, Fife and colleagues evaluated the use of TcPO2 in 1144 patients. In this study, predictive values were relatively poor, with some patients healing despite low initial and in-chamber TcPO2. 42

While data, particularly recently, have pointed toward HBO therapy as having some degree of potential benefit, its cost is high. Patients often travel long distances for daily treatments at great cost to themselves and their families. Although reported protocols for treatment of ischemic limb ulcers vary significantly, most involve a total cost of $15,000 to $40,000. In an assessment for the Canadian
government, Chuck et al from the University of Alberta compared HBO and standard care for DFUs using a decision model and available outcomes data. They found that the average yearly cost for HBO treated ulcers was $40,695 (Canadian) compared with $49,786 (Canadian) for standard care. They concluded that adjunctive HBO is cost-effective compared with standard care alone.43

Currently, HBO is an option that may improve limb preservation in a limited group of patients with complicated ischemic and diabetic limb ulcers. Other HBO indications reimbursed by most insurers include the treatment of inhalation injury, necrotizing wound infections, crush injury, and osteoradionecrosis. Until larger randomized studies are performed, it cannot be recommended as a primary treatment for patients with uncomplicated diabetic or ischemic ulcers. But in selected more complicated cases, HBO may have a role.

WOUND TREATMENTS ON THE HORIZON

Stem cell therapy. Marrow cells have been shown to play an important role in the healing of cutaneous wounds. Subsequent to dermal wounding, marrow-derived mesenchymal stem cells (MSC) are mobilized into the peripheral circulation and engraft near adnexal structures in the skin. These cells eventually differentiate into skin cells.44 Deng et al transplanted fluorescent-labeled bone marrow MSC into lethally irradiated mice and found that labeled cells gave rise to stem cells and committed cells in the skin.45 Another study found that 15% to 20% of the dermal fibroblasts originated from the bone marrow in a murine wound model.46 Animal studies have shown wound healing significantly improved after injection of MSC into the wound.47 Bauer et al found that although extremity ischemia is a powerful stimulant for marrow stem cell recruitment, fewer progenitor cells were able to migrate to the ischemic wound.48 This may be a result of macro- and microvascular disease, obstructing vascular conduits for mobilization of MSC. Local application, topically or via injection, of MSC would place these progenitor cells at the site of injury, assisting in homing and delivery. Human studies with recent small case-series transplanting autologous cultured marrow derived MSC and pure marrow aspirate (Fig 4) have shown rapid improvement in granulation and healing in chronic wounds.44,49,50

Badiavas and Falanga44 harvested bone marrow aspirate from the ileum in three patients with chronic wounds unresponsive to aggressive therapy (abdominal dehiscence, lower extremity arterial ulcer, and lower extremity venous ulcer) and injected the marrow aspirate into the peri-wound tissue and applied the aspirate topically. The remaining aspirate was cultured and expanded in vitro and later applied topically to the wounds in a repeat treatment. The authors noted that, after each treatment with cultured MSC, the wounds experienced a burst of granulation tissue. Two patients healed rapidly by secondary intention; one patient healed with the use of a skin substitute (cultured fetal foreskin). They concluded that their study supported the hypothesis that bone marrow aspirate contained progenitor cells that can engraft into wound and accelerate healing.

Other critical considerations. Despite the plethora of advances, results from a myriad of published and unpublished industry-sponsored, randomized trials that evaluated the efficacy of these advanced wound healing agents have been less than ideal and are difficult to place in perspective.5,51-53 For example, published healing rates for DFUs treated by TCCs (total contact casts) are noted to be 80% to 90% compared with only 45% to 55% for biologic tissues.54,55 Most studies either offered shoes or sandals to study participants or allowed individual centers to select the type of pressure relief;55 however, not one of these studies employed irremovable offloading.

Such considerations emphasize the importance of using advanced wound healing modalities as adjuvant therapies that work synergistically with standard wound care regimens such as routine debridement, pressure mitigation, infection control, and provision of adequate vascularity to the affected area. Without adhering to these important principles, the addition of any adjunctive modality is unlikely to result in improved healing rates.1,13 Wound bed preparation encompasses the removal of necrotic tissue,
formation of granulation tissue, and elimination of wound exudate. Brem et al. found that two separate clinical and specialty sites were able to achieve a frequency of complete wound closure of greater than 70% within 6 months via optimal wound preparation. Care for a patient with diabetic foot ulceration is complex, necessitating collaboration of a multidisciplinary team to achieve treatment goals; such a team must accurately assess and manage current wound and patient conditions, optimally manage subsequent complications, and aim to promote shorter healing time. Advanced wound healing modalities, when used appropriately, may serve as useful components of the wound management algorithm.

REFERENCES


45. Deng J, Petersen BE, Steindler DA, Jorgensen ML, Laywell ED. Mesenchymal stem cells spontaneously express neural proteins in culture and are neurogenic after transplantation. Stem Cells 2006;24:1054-64.


