Wound Healing: Part II. Clinical Applications

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Learning Objectives: After studying this article, the participant should be able to: 1. Identify effective methods for irrigation and débridement of wounds. 2. Describe methods for optimal closure of a wound. 3. Develop an algorithm for postoperative scar management. 4. Appreciate adjunctive clinical tools that may facilitate improvements in wound healing.

Summary: Treatment of all wounds requires adequate wound bed preparation, beginning with irrigation and débridement. Complicated or chronic wounds may also require treatment adjuncts or specialized wound healing products. An extensive body of research and development has introduced novel wound healing therapies and scar management options. In this second of a two-part continuing medical education series on wound healing, the reader is offered an update on current wound healing technologies and recommendations for obtaining optimal outcomes. (*Plast. Reconstr. Surg.* 133: 383e, 2014.)

While healing of any wound begins with surgical preparation and basic wound care principles, complex wounds may require special treatment adjuncts or wound care products. Care of these complicated wounds often falls to the plastic surgeon but is relevant to all practitioners presented with the acute or chronic wound. In this second part of a two-part continuing medical education series on wound healing, key features of clinical management of wounds and guidelines for optimal closure are explained.

WOUND PREPARATION

Irrigation

Standard practice before wound closure is assurance of a clean wound bed. This often begins with irrigation. Seemingly without rhyme or reason, surgeons poke holes in a bottle of saline, squirt the wound with a Toomey syringe, or connect 3 liters of fluid to irrigation tubing. Although the removal of foreign bodies and gross contamination is advisable, there is little evidence to support the use of one lavage fluid over another. In a multicenter, randomized, blinded pilot trial of open fractures treated with either normal saline or castile soap solution, no difference in infection, wound healing problems, or nonunion was seen.[1] Although some patients and practitioners balk at the use of tap water to clean a wound, multiple studies have supported its safety.[2,3]

While the selection of irrigation fluid is of less concern, irrigation technique may have an impact on wound healing. High-pressure (50-psi) pulsatile jet irrigation may reduce bacterial loads more efficiently than gravity flow or bulb syringe irrigation.[4] Some studies report that high-pressure syringe irrigation is also more effective than bulb syringe irrigation in reducing bacterial contaminants and decreasing the number of subsequent wound infections.[5,6] However, conflicting studies in animal models do suggest that higher pressure causes soft-tissue damage[7] and may force bacteria into soft tissue.[8] A randomized controlled trial investigating the optimal pressure and lavage fluid for irrigation has completed its pilot study and should offer additional clarification on this controversy.[1] Preliminary results suggest that low-pressure pulsatile lavage may decrease the reoperation rate due to infection, wound healing problems, and nonunion in an open fracture wound.

Antiseptics

Topical antiseptics are antimicrobial agents used to reduce or inhibit the number of microorganisms on living tissue. Although the merits of their use are logical, there have also been reports of their inhibitory effects on wound healing,

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especially in open wounds. Iodine is known to be bactericidal and is commonly used as povidone-iodine, a water-soluble complex. Animal studies have shown fairly consistent delay in wound healing and variable reduction in bacterial loads.[9] Human studies, however, have not shown any reduction or prolongation of wound healing.[10,11] It also offers antimicrobial advantages, as it is effective against many bacteria, including *Pseudomonas* species and *Staphylococcus aureus*.[12]

Compared with iodine, higher concentrations of hydrogen peroxide may be required for antisepsis, due to the high concentration of catalase produced by some bacteria.[13] It has also been suggested that hydrogen peroxide potentially retards the migration and proliferation of fibroblasts.[14] However, other studies have suggested that low levels of hydrogen peroxide may stimulate cell migration and wound healing by producing reactive oxygen species.[15,16] Chlorhexidine exerts its antibacterial effects through disruption of microbial cell membranes and precipitation of cell contents. It is more effective against Gram-positive than Gram-negative bacteria, and has poor antifungal effects.[13] A meta-analysis that included 5031 patients supports its reduction in postoperative surgical-site infections and recommends its used preferentially over povidone-iodine in clean-contaminated operations (**Level of Evidence: Therapeutic, II**).[17] Its use should be restricted to immediate preoperative cleansing, as whole-body preoperative chlorhexidine showers do not significantly affect infection rates (**Level of Evidence: Therapeutic, II**).[18]

Débridement

Irrigation and topical antiseptics are of little assistance in the removal of necrotic tissue, biofilms, or gangrene. Resection of nonviable tissue back to healthy, bleeding wound is necessary for wound healing. Sharp dissection and the use of a scalpel, scissors, curette, or rongeur are simple and cost effective. End points are healthy skin edges with bleeding, dense dermis; viable, soft, yellow subcutaneous fat; solid tendon substance; red bleeding muscle; and hard, healthy bleeding bone with pinpoint bleeding, known as the paprika sign. Care should be taken to preserve healthy surrounding tissues, by use of an atraumatic technique and frequent changes of the surgical blades. Attinger et al. suggest the use of a Cobb elevator (Fig. 1, *left*) for exposing bone and McElroy curettes (Fig. 1, *right*) for débridement of chronic granulation tissue in deep cavities.[19]

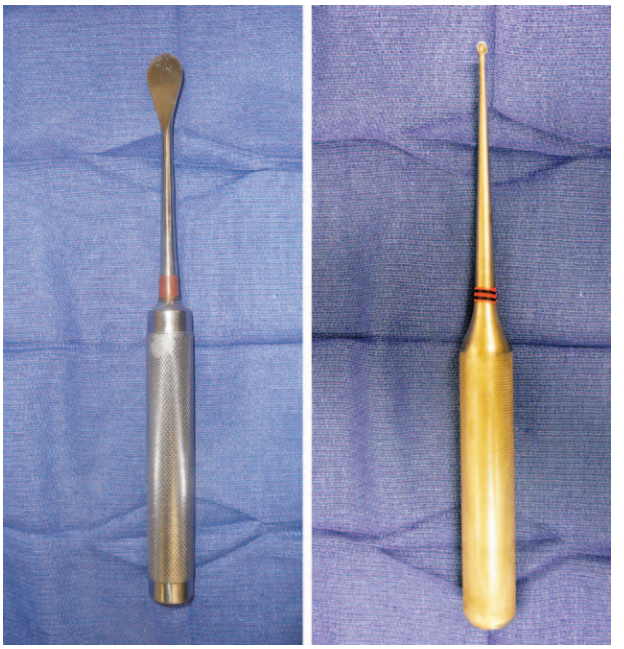
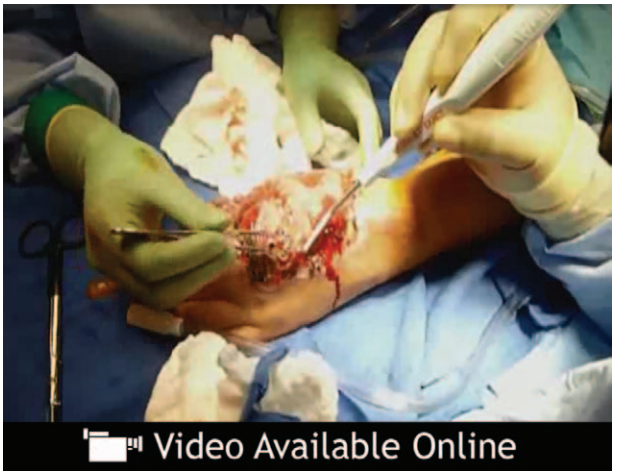


Fig. 1. (*Left*) The Cobb elevator. (*Right*) The McElroy curette.

Débridement can also be performed with high-pressure lavage, although this is typically more effective after sharp débridement has been performed. First described for burn débridement, the Versajet (Smith & Nephew, Cambridge, England) uses a pressurized stream of water and a vacuum around this stream (Venturi effect) to remove the surrounding tissue.[20] (**See Video, Supplemental Digital Content 1**, which demonstrates use of the



Video 1. Supplemental Digital Content 1 demonstrates use of the Versajet for efficient wound débridement. Pearls to obtain maximal benefit from this device are included in the video. This video is available in the "Related Videos" section of the full-text article on PRSJournal.com or, for Ovid users, at ***http://links.lww.com/PRS/A945***.

Versajet for efficient wound débridement. Pearls to obtain maximal benefit from this device are included in the video. This video is available in the "Related Videos" section of the full-text article on PRSJournal.com or, for Ovid users, at ***http://links.lww.com/PRS/A945***.) Due to its small size and easy handling, it is particularly effective in areas such as the face, hand, and foot. Studies done on wound biofilms in a polymicrobial porcine model have shown an almost 1000-fold reduction in bacterial colonies using the Versajet and significant reductions in inflammatory neutrophil markers[21] (Fig. 2). Its cost effectiveness is debated, but reductions in operating time compared with conventional surgical débridement suggest potential cost savings with its use.[22,23]

When sharp débridement is not an option, conservative management with enzymatic débridement has proven effective in removing slough and eschar. Collagenase (Santyl; Smith and Nephew, Inc., Largo, Fla.) shows more rapid removal of necrotic tissue over placebo,[24–26] and was shown to be superior to silver sulfadiazine in partial-thickness burn wounds.[27] Unlike collagenase, papain has no effect on collagen, breaking down only proteins containing cysteine residues. The combination of papain and urea (Accuzyme; Healthpoint Ltd., Fort Worth, Texas) facilitates

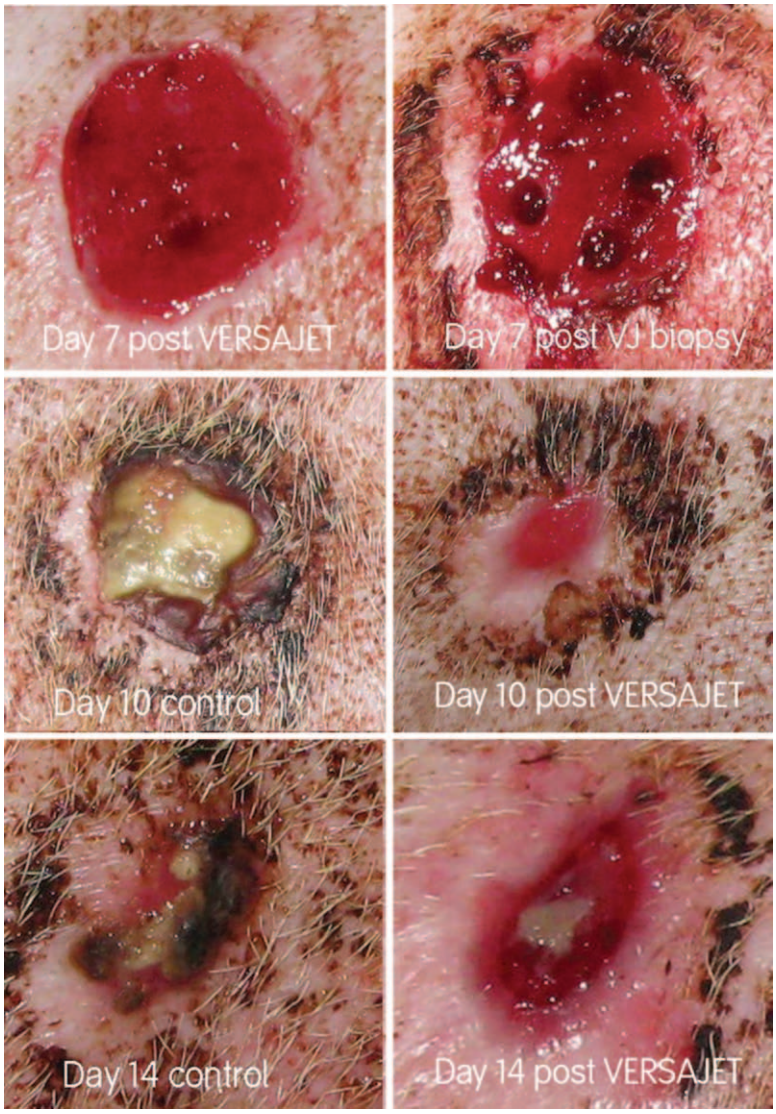


Fig. 2. Changes in wound appearance with and without Versajet débridement on days 7, 10, and 14. Adapted and reprinted with permission from Allan N, Olson M, Nagel D, Martin R. The impact of hydrosurgical debridement on wounds containing bacterial biofilms. *Wound Rep Regen.* 2010;18:A88.

protein breakdown, as urea alters the three-dimensional structure of proteins and disrupts hydrogen bonds.[28] Papain-urea can be painful on application, however, and is not effective when combined with some commonly used wound care products, such as silver sulfadiazine and hydrogen peroxide.

While seldom preferred by patients, maggot débridement therapy has shown a recent resurgence due to the swift débridement and relatively low cost. The benefits of maggot therapy were recognized hundreds of years ago by military surgeons who noticed that injured soldiers healed better when their wounds were infected with maggots. An orthopedic surgeon, William Baer, suggested that maggots assist with wound healing by clearing away fragments of bone and tissue slough, but there is some evidence that maggots also possess antimicrobial properties against methicillin-resistant *S. aureus*, *Pseudomonas aeruginosa*, vancomycin-resistant *Enterococcus* species, and *Candida albicans*.[29] Maggots are preferentially used for necrotic, wet, or exudative wounds, as they need a moist environment to survive. Specific indications for their use include pyogenic osteomyelitis, carbuncles, necrotic gangrenous wounds, diabetic foot ulcers, syphilitic ulcers, pyoderma gangrenosum, and necrotic skin cancers.[30]

WOUND CLOSURE

Suture

Once the wound has been prepared and is ready for closure, the proper suture and suture technique must be selected. Wounds may be closed with simple interrupted, horizontal mattress, vertical mattress, figure-of-eight, or running sutures. The choice of the closure technique should not be arbitrary but should be based on wound and patient characteristics. Simple interrupted sutures are excellent for precise alignment of wound edges. Horizontal and vertical mattress sutures are effective in relieving tension from the wound edges and for tissue eversion, but they can cut into the skin and compromise blood supply.[31] The figure-of-eight suture can be used to close two layers simultaneously, reduce round or elliptical defects, or secure a nail plate after nailbed repair (Fig. 3). Running sutures are quickly placed and provide hemostasis, especially in scalp wounds.

When selecting the optimal suture for wound closure, one must consider patient age, wound characteristics, wound location, and potential for follow-up. Suture diameter is expressed by the number of zeros, with more zeros indicating a smaller suture size. However, suture diameter also depends on suture characteristics, so that a 6-0 gut suture will be larger than a 6-0 polypropylene suture. Multifilament sutures are braided and allow for easier handling, but they may increase the rate of wound infection because bacteria can hide among the filaments.[32,33] Their use should be avoided in contaminated wounds. Recently, triclosan-impregnated sutures have been introduced in an effort to decrease surgical-site infections, but their efficacy has been questioned. Their use in cardiac surgery demonstrated no advantage in the reduction of sternal wound infections and are associated with a higher cost.[34] A systematic review also failed to show a statistically significant reduction in the rate of surgical-site infections.[35]

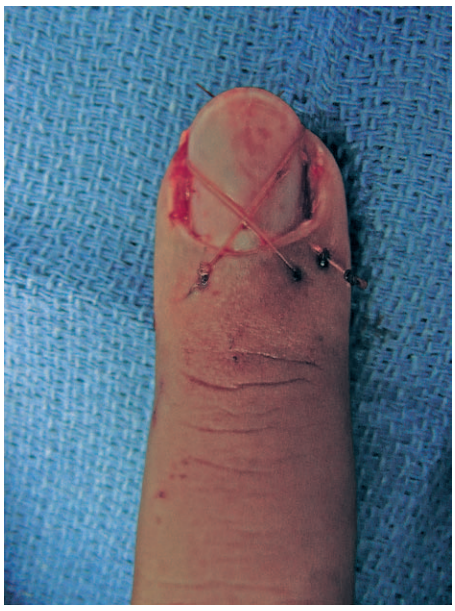


Fig. 3. A figure-of-eight suture is used to secure the nail plate for nailbed repair.

Sutures may be absorbable or nonabsorbable. Absorbable sutures are convenient for buried suturing or in pediatric patients who do not tolerate suture removal. Attention should be paid to the estimated time to resorption, as the suture may or may not provide adequate support during the healing process. Catgut, for example, retains its strength for 4 to 5 days and should not be relied upon in areas of tension. Polydioxanone is absorbed after approximately 180 days, thereby corresponding with the time of maximal wound strength. When compared with polyglycolic acid, which is absorbed in 90 to 120 days, polydioxanone resulted in less scar widening and less scar hypertrophy at 6 months (**Level of Evidence: Therapeutic, II**)[36] (Table 1). Recently, tissue adhesives have been popularized

Table 1. Suture Characteristics*

Suture	Handling	Time to Degradation	Knot Security	Memory	Tissue Reactivity
Gut	Excellent	60–90 days	Poor	Low	Moderate
Polyglycolic acid	Good	90–120 days	Fair	Low	Moderate
Polyglactin	Good	60–90 days	Fair	Low	Low
Polydioxanone	Poor	180–210 days	Poor	High	Low
Poliglecaprone	Excellent	90–120 days	Good	Low	Low
Silk	Excellent	50% strength loss per year	Excellent	Low	High
Nylon, monofilament	Poor	15–20% strength loss per year	Poor	High	Low
Nylon, multifilament	Fair	15–20% strength loss per year	Fair	Medium	Moderate
Polyester	Good	Nonabsorbable	Good	Medium	Low
Polypropylene	Poor	Nonabsorbable	Poor	High	Low
Polybutester	Good	Nonabsorbable	Fair	Low	Low

*Adapted from Tajirian A, Goldberg D. A review of sutures and other skin closure materials. *J Cosmet Laser Ther.* 2010;12:296–302.

by their ease of application. They obviate the risk of needlestick injury and eliminate the need for suture removal. In wounds that are not under tension, tissue adhesives perform equivalently for cosmetic outcomes.[37–39] Care should be taken when applying tissue adhesive in wounds under tension, as sutures are significantly better at preventing wound dehiscence (**Level of Evidence: Therapeutic, II**).[40]

Scar Management

Two of the most frequent questions posed to the plastic surgeon are, "Will I have a scar?" and "How can I make my scar look better?" Except in fetuses and amphibians, incisions through the dermis will always produce a scar, but exacting suture placement and postoperative care can minimize its appearance. A comprehensive review of evidence-based recommendations published by Mustoe et al. emphasizes the efficacy of silicone gel sheeting.[41] Silicone gel sheeting is recommended as soon as epithelialization is complete, and its use should be continued for at least 1 month. Although no prospective trials have demonstrated its efficacy, hypoallergenic taping is cheap and may also be used in the postoperative period. Success with silicone gel sheeting has been seen in at least eight randomized controlled trials but depends on early application and use for at least 12 hours a day.[42] Patient compliance, therefore, may be difficult. Although the exact mechanism of action of silicone gel is not known, proposed mechanisms include increases in temperature and collagenase activity, increased hydration, and polarization of the scar tissue leading to scar shrinkage.[43]

Scars not successfully managed with silicone gel sheeting may be candidates for corticosteroid injections. Mustoe et al. recommend 2.5- to 20-mg/ml injections for the face and 20- to 40-mg/ml injections for the body, which can be repeated monthly if necessary.[41] Corticosteroids decrease collagen synthesis and limit fibroblast proliferation, but they can also lead to subcutaneous atrophy, telangiectasias, and pigment changes.[44] As monotherapy for hypertrophic or keloid scars, their efficacy ranges from 50 to 100 percent, but scar recurrence is common. Higher success rates are obtained when corticosteroids are combined with other treatments, such as surgery, 5-fluorouracil, or radiation.[45]

For the less problematic scar, noninvasive methods, such as pressure garments, have been recommended. The mechanism of action of pressure garment therapy is unknown, but a decrease in edema or reduction in blood flow and collagen synthesis may be responsible for the reduction in scar thickness seen in some studies.[46,47] A meta-analysis of six trials showed a small improvement in scar height with pressure therapy, but the study failed to demonstrate an improvement in global scar scores. Mechanical pressure through massage has also been recommended, but support for its use is weak. Treatment protocols vary and outcomes are not standardized. However, its use after primary closure has been obtained is relatively innocuous and may be effective in decreasing pain and increasing a sense of well-being.[48]

Massage has been combined with topical vitamin E, which is easily obtained at drugstores and proposed to inhibit fibroblast proliferation and inflammation. Most studies do not support an improved cosmetic appearance of scars treated with vitamin E,[49,50] and its use may cause urticaria and eczema associated with contact dermatitis (**Reference 50, Level of Evidence: Therapeutic, II**). Topical onion extract (Mederma; Merz Pharmaceuticals, Greensboro, N.C.) is also a common ingredient in some over-the-counter scar management products. In a rabbit hypertrophic scar model, it demonstrated improvement in dermal collagen organization, but there was no reduction in scar hypertrophy

or scar elevation.[51] A prospective, randomized, double-blinded, split-scar study comparing it with petrolatum-based ointment also found no difference in scar erythema, hypertrophy, or overall cosmetic appearance.[52]

TREATMENT ADJUNCTS

Hyperbaric Oxygen

Hyperbaric oxygen therapy takes advantage of the ability to saturate dissolved oxygen levels in plasma by placing the patient in a pressurized chamber of 100% oxygen. By creating wound hyperoxia, hyperbaric oxygen is thought to stimulate neovascularization in the now relatively hypoxic wound bed and assist with oxidative microbial killing and wound matrix repair.[53] It has been described for the treatment of wounds associated with peripheral vascular disease, diabetes, radiation necrosis, osteomyelitis, and soft-tissue infections. The most evidence exists for its use in diabetic foot wounds, where it has been found to significantly reduce the risk of major amputation and improve healing,[54] and in mandibular osteoradionecrosis, where it may help close fistula tracts, decrease the amount of exposed bone, and obtain complete closure.[55,56] Research on its use for peripheral nerves also shows preliminary evidence of improvement in functional recovery following microsurgical repair, although further human investigation is needed.[57,58]

Platelet-Rich Plasma

The wave of enthusiasm for platelet-rich plasma has advertised its success in nerve injury, tendinitis, osteoarthritis, bone repair, and tissue regeneration. Essentially, platelet-rich plasma is a high concentration of platelets suspended in a small amount of plasma, resulting in a high concentration of growth factors. This high concentration of growth factors is held responsible for the ability of platelet-rich plasma to stimulate wound healing. It has achieved celebrity status through its use in professional athletes, but many studies suffer from lack of controls or limited sample size.

Although most studies have been performed on nonhuman subjects, the first prospective, randomized, controlled multicenter trial in the United States to study the use of platelet-rich plasma gel for the treatment of diabetic foot ulcers showed that it increased the rate of healing and reduced the time to complete healing.[59] However, 32 of 72 patients were excluded before final analysis due to protocol violations and failure to complete treatment. In addition, ulcers with exposed tendon or bone, patients with mild to moderate vascular disease, and patients with hyperglycemia or inadequate nutritional status were excluded. The use of platelet-rich plasma in bony healing has been reported in the orthopedic and oral surgery literature, but again, prospective, randomized human studies are lacking.[60]

In addition to the lack of high-level evidence for its use, platelet-rich plasma is subject to high variability based on its method of production. Table-top centrifuge, cell separators, and selective filtration have been used, and their effect on the product is unknown. More data are required before conclusions can be drawn about the success of platelet-rich plasma and the indications for its use.

Stem Cells

Similar enthusiasm has been seen for the use of stem cells in wound healing, as it seems only logical that pluripotent cells would be able to contribute to the regeneration of skin, bone, and cartilage. Their success in cardiac[61] and neural regeneration[62] has been promising, and a large body of research continues worldwide. Bone marrow–derived stem cells have resulted in reconstitution of fully differentiated hair-bearing skin in nude mice[63] and enhanced granulation tissue formation and vascularization in a diabetic mouse model.[64] Human models are limited, but the only randomized controlled trial to use bone marrow stem cells in nonhealing lower extremity ulcers reduced wound size and increased pain-free walking distance.[65]

Although there is no level I evidence regarding the use of stem cells in fracture nonunion or delayed union, local application of bone marrow concentrate has produced new bone formation in several clinical series.[66,67] Bone marrow–derived stem cells on hydroxyapatite scaffolds have also been used in patients with segmental defects of the tibia, humerus, and mandible.[68,69] At this point, clinical results are still limited by small sample sizes, lack of controls, and short follow-up, but bone tissue regeneration appears promising.

Adipose tissue is one of the richest sources of mesenchymal stem cells, and multiple clinical trials are currently underway to examine their use in bone tissue repair, diabetes, autoimmune disease, and neurologic disorders.[70] In 2007, 20 patients with radiation wounds were treated with purified lipoaspirate, and an improvement in tissue wound healing was observed. Akita et al. reported the use of a combination of adipose-derived stem cells, human recombinant basic fibroblast growth factor, and artificial skin substitute to successfully treat

an intractable sacral wound, but the results were clouded by the multimodal therapy.[71] Although promising, clinical use of adipose-derived stem cells in the United States is necessarily limited by requirements of a rigorous review by the U.S. Food and Drug Administration and compliance with Current Good Tissue Practice requirements.

Honey

In contrast to the novel, costly, and yet-unproven stem cell and platelet-rich plasma therapies described above, honey offers a cheap, effective topical treatment for wounds. Honey was used for medicinal purposes by the ancient Greeks and Egyptians, including the famed Hippocrates.[72] While it cannot claim to regenerate tissues or heal bony defects, honey does facilitate wound healing and suppress microbial proliferation. Its antibacterial effects are attributed to honey's acidity, hydrogen peroxide content, and high osmolality.[73] A meta-analysis of 624 subjects also supports the greater efficacy of honey compared with alternative dressings, but cites multiple studies being performed by the same investigator as a limiting factor in the analysis.[74] Its antimicrobial properties also make honey attractive for use in infected wounds. Multiple studies have reported on its effectiveness in this regard, citing complete resolution of methicillin-resistant *S. aureus* with its use.[75–78] The exact amount of honey needed for antibiosis and wound healing is unknown, however, and the composition and geographical origin of the honey may influence its medicinal value. Currently, the only line of honey-based wound dressings approved by the Food and Drug Administration is Medihoney (Derma Sciences, Inc., Princeton, N.J.), which relies on manuka or *Leptospermum* honey combined with an absorbent seaweed-based material.

NEGATIVE-PRESSURE WOUND THERAPY

After four failed journal submissions and three rejections from national meetings, a 1997 article by Drs. Argenta and Morykwas[79] initiated what was to become a paradigm shift in the treatment of open wounds. This article described the use of a vacuum-assisted closure device to treat 296 wounds that resulted in an increased rate of granulation tissue formation, decreased edema, and increased localized blood flow.

Suggested pathophysiological responses to negative-pressure wound therapy include mechanotransduction, removal of tissue exudate, increases in tissue perfusion, and reduction in bacterial bioburden.[80] By exerting tensile forces on the local tissue environment, vacuum devices are thought to create cellular deformation that results in mitotic activity and cell proliferation.[81,82] Negative-pressure wound therapy conveniently manages wound fluid exudate, thereby minimizing dressing changes and maintaining a clean environment for patients and nursing personnel. By removing this exudate, the device is also thought to minimize exposure to bacteria, inflammatory cytokines, and matrix metalloproteinases that can otherwise contribute to the formation of a chronic wound.[83,84]

The increase in granulation tissue seen after institution of negative-pressure wound therapy suggests that increases in perfusion to the wound are occurring simultaneously. Perhaps due to variations in measurement techniques and in the locations of measurements, studies have shown mixed results for microvascular blood flow in wounds treated with negative-pressure wound therapy.[85–87] Results on bacterial clearance provided by negative-pressure wound therapy largely conclude that bacterial clearance is not the mechanism of action. In fact, multiple studies report increased colonization with vacuum-assisted therapy,[88–90] although this might not affect final wound closure.

Contraindications to its use do exist, however. Negative-pressure wound therapy is not recommended in the setting of exposed vessels, malignancy, necrotic tissue, untreated osteomyelitis, or nonenteric and unexplored fistulas.[91] Extreme caution should be exercised in patients receiving anticoagulation therapy or those with active bleeding or grossly infected tissues. Sharp débridement remains the accepted standard for infected tissues. The U.S. Food and Drug Administration has issued a safety communication on serious complications associated with negative-pressure wound therapy in which bleeding is reported as the cause of most serious adverse events. Cases of critical infections were largely related to the retention of dressing pieces in the wounds and occurred more commonly at home or in a long-term care facility.[92] Health care providers are advised to keep track of the number of dressing pieces placed in the wound and to not cut the dressing directly over the wound, in order to avoid fragments falling into the wound. Patients and caregivers should receive appropriate training on the use of the device and be alert for warning signs of potential complications. (**See Video, Supplemental Digital Content 2**, which demonstrates the appropriate application of the vacuum-assisted wound closure device and describes recommendations for its use. This

Video 2. Supplemental Digital Content 2 demonstrates the appropriate application of the vacuum-assisted wound closure device and describes recommendations for its use. This video is available in the "Related Videos" section of the full-text article on PRSJournal.com or, for Ovid users, at ***http://links.lww.com/PRS/A946***.

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SUMMARY

Research and technology in wound healing are constantly advancing. It behooves the plastic surgeon, who should be considered an expert in wound healing, to also maintain proficiency in current methods and technologies available for healing wounds. Given the rapid progress occurring in this field, this will require continual review of the literature and appropriate clinical and practice adaptations.

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