State of the Art in Topical Wound-Healing Products

Kenneth Fan, B.S.
Jennifer Tang, B.S.
Julia Escandon, M.D.
Robert S. Kirsner, M.D., Ph.D.
Miami, Fla.

**Summary:** Chronic wounds represent a significant medical burden. Such wounds fail to normally progress through the stages of healing, often complicated by a proinflammatory milieu caused by increased proteinases, hypoxia, and bacterial burden. As a result, several modalities, such as dressings, antimicrobials, growth factors, and human skin substitutes, have been devised in an attempt to correct the chronic wound environment. This review addresses these modalities with a focus on evidence and randomized controlled trials. (Plast. Reconstr. Surg. 127 (Suppl.): 44S, 2011.)

**RATIONALE FOR TOPICAL TREATMENT**

Chronic wounds are a medical challenge, costing the U.S. health system over $25 billion dollars per year. Leg ulcers alone affect upward of 2.5 million Americans, with 2 million workdays lost per year. Two-thirds of patients report negative emotional impact directly attributable to their ulcer, illustrating the necessity for proper wound care. Although the causes of chronic wounds are numerous, diabetic, arterial, venous, and pressure ulcers constitute the majority of chronic wounds. Despite unique pathophysiology, factors contributing to chronicity of nonhealing wounds become similar with time (Fig. 1).

**BIOLOGY OF CHRONIC WOUNDS**

Wound healing is a dynamic process of three overlapping phases: inflammation, proliferative phase with granulation tissue formation and epithelialization, and tissue remodeling. Inflammation lasts several days in the acute healing wound but persists in the chronic wound. Driven by proinflammatory cytokines, the prolonged and overactive neutrophil response leads to increased protease activity, mainly matrix metalloproteinases. In some cases, protease activity has been found to be over 100 times higher in chronic compared with acute wounds. Increased metalloproteinases lead to degradation of growth factors, their receptors, and adhesion proteins, such as fibronectin and vitronectin, preventing cell adhesion for normal wound closure. As a result, topical treatments aimed at inflammation and excess proteases have been developed.

Wounding damages the blood supply, leading to hypoxia, along with subsequent decreased oxidative bursts and microbicidal activity by polymorphonuclear leukocytes. The uncontrolled polymorphonuclear leukocytes respond to low oxygen tension by releasing proteinases and toxic oxygen metabolites, which damages endothelial cells, leading to cellular destruction, deposition of fibrin, and further decreased delivery of nutrients and oxygen, propagating a vicious cycle. Systemic disorders, such as decreased cardiac output, smoking, peripheral vascular disease, past irradiation, and chronic infection, all contribute to hypoxia in the local environment. Reperfusion injury plays a role. During ischemia, substances such as hypoxanthine and xanthine oxidase are made. Reperfusion causes oxygen to react with these substances, producing superoxide bursts that further damage the endothelium.

The inflammatory state is also prolonged by the presence of bacteria, leading to increased metabolic demand and protease levels in the wound. The mere presence of bacteria in chronic wounds does not affect healing. Definitions used for overt, clinical infection include microorganism density greater than $10^5$ to $10^6$ colony-forming units/g, as these levels are used as a threshold for delayed wound healing and disease. Symptoms such as...
exudate, odor, pain, change in color and texture of tissue, wound deterioration, and rapid onset of slough tissue herald increasing bacterial burden. However, infection should be considered if the wound simply fails to heal, as symptoms are not always reliable.

Corticosteroids, immunosuppression, diabetes, liver cirrhosis, and undernourishment may serve to suppress the immune system, increasing the risk of infection. Malnourishment also deprives the patient of essential vitamins and proteins necessary for proper healing. Insufficient blood flow, seroma, necrosis, hematoma, and other local factors further increase the risk of infection. The presence of foreign materials and necrotic tissue greatly decreases the amount of bacteria necessary for wound infection. Dressings and surgical techniques for débridement of these foreign materials are available to the surgeon.

**DRESSINGS**

Two general categories of wound dressing exist. Passive wound dressings mainly control wound moisture levels. The synthetic polymers in dressings afford customization in terms of absorbency, physical form, and gas permeability (Table 1). Active dressings locally alter the wound’s biochemical environment.

**Passive Dressings**

The rationale for occlusive dressings is often traced to 1962, when Winter observed that moisture-retaining dressing speeds epithelization of acute, superficial compared with air-exposed wounds in pigs. The following year, Hinman and Miabach published results in humans demonstrating similar results. The benefits of occlusion in partial-thickness wounds are numerous. Without the impediment of the crust seen in dry wounds, the wet dermal surface provides a superior medium for epidermal cells to migrate. Eaglstein and Mertz demonstrated that occlusion accelerates epithelialization in the acute split-thickness wound by 40 percent. Acute wound fluid under the occlusive bandage contains substances, such as growth factors, that stimulate proliferation of fibroblasts and endothelial cells, promoting granulation tissue formation.
### Table 1. Available Passive Dressing Types*

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
<th>Discharge Amount</th>
<th>Indications</th>
<th>Advantage</th>
<th>Disadvantage</th>
<th>Examples of Available Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alginates</td>
<td>Produced from brown seaweed; either 100% calcium alginate or 80:20 calcium alginate to sodium alginate; fibrous gel is formed when calcium in the dressing exchanges with sodium from the wound; absorbs 20 times of weight; nonocclusive; requires secondary dressing; loose rope or pad forms. Examples of Available Products: Alginates Produced from brown seaweed; either 100% calcium alginate or 80:20 calcium alginate to sodium alginate; fibrous gel is formed when calcium in the dressing exchanges with sodium from the wound; absorbs 20 times of weight; nonocclusive; requires secondary dressing; loose rope or pad forms.</td>
<td>Heavy</td>
<td>Moderate to heavy exudate in superficial to deep wounds; autolysic débridement; rope form to pack deep or tunneling wounds; infected wounds</td>
<td>Conformable; allows gas exchange along with protection from contamination; draws out contaminates and excess exudate in heavily draining wounds.</td>
<td>May dehydrate wounds with minimal exudate; contraindicated in third-degree burns; not recommended for dry eschar or light exudate; as it may adhere and cause pain on removal; need to be changed daily.</td>
<td>Algicell Calcium Alginate (Dermasciences, Princeton, N.J.); Algiderm (Bard Medical, Covington, Ga.); CURASORB (Kendall, Dublin, Ireland); Kaltostat (Convatec, Skillman, N.J.); Melgisorb (Mölnlycke, Göteborg, Sweden); Tegaderm (3M, St. Paul, Minn.)</td>
</tr>
<tr>
<td>Foams</td>
<td>Air bubbles in a matrix of polyurethane or silicone capable of holding or releasing fluids; highly absorbent while maintaining moisture; provides thermal insulation; dressings can be applied as sheets or liquid; some require secondary dressings. Examples of Available Products: Foams for Dressings.</td>
<td>Moderate</td>
<td>Moderate to heavy exudate in superficial to deep wounds; autolysic débridement; padding and protection in high trauma areas; infected wounds; under compression dressing.</td>
<td>Silicone liquid form is conformable to the wound; nonlimiting facilitates atraumatic removal; polyurethane foam provides uniform dispersion of exudate in absorbant layer with semipermeable backing prevents strike-through, which is when exudates permeate dressings, providing an entry point for bacteria.</td>
<td>Does not conform well to deep cavity or sinus tracts; may dehydrate wounds with minimal exudate; may promote maceration if saturated.</td>
<td>Allevyn Foam (Smith &amp; Nephew, London, United Kingdom); Contreet Foam (Coloplast, Minneapolis, Minn.); CURAFOAM (Kendall, Dublin, Ireland); Hydrocell Foam (Dermasciences, Princeton, N.J.); Invacare Foam (Invacare Supply Group, Elyria, Ohio); LYOFOAM (Mölnlycke, Göteborg, Sweden); Mepilex (Mölnlycke); Versiva (Convatec, Skillman, N.J.)</td>
</tr>
<tr>
<td>Transparent film</td>
<td>Thin sheet of polyurethane film; semipermeable, variable water vapor transmission rate; impermeable to bacteria or fluids. Examples of Available Products: Transparent Dressings.</td>
<td>Scant</td>
<td>Dry wounds to maintain moisture; IV site protection; autolysic débridement; secondary dressing</td>
<td>Barrier against bacteria and contaminants; binds tightly leading to protection of high-friction areas; flexible, can be placed over joints.</td>
<td>No absorbency; fluid can accumulate; break adhesive seal, and cause infection and maceration; required border of intact skin may be torn by adhesives; problematic with fragile skin; adherent material can come in contact with wound and tear off epithelialized skin.</td>
<td>Comfeel Film (Coloplast, Minneapolis, Minn.); OpSite (Smith &amp; Nephew, London, United Kingdom); Polyskin (Kendall, Dublin, Ireland); ReliaMed Transparent Film (ReliaMed, Fort Worth, Texas); Tegaderm (3M, St. Paul, Minn.)</td>
</tr>
</tbody>
</table>

(Continued)
<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
<th>Discharge Amount</th>
<th>Indications</th>
<th>Advantage</th>
<th>Disadvantage</th>
<th>Examples of Available Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocolloids</td>
<td>Mixture of materials such as gelatin, pectin, polycarboxymethylcellulose, elastomers bonded to a semipermeable film or a foam sheet; highly occlusive; brown, self-adherent surface; usually waterproof; absorbs moisture slowly; available in sheet form or paste/granules to fill deep wounds</td>
<td>Minimal</td>
<td>Light to moderate exudate in shallow full-thickness defects; wounds requiring moisture, such as granulation tissue; used under compression dressing; autolytic débridement, especially with necrotic, dry eschar</td>
<td>Available in ultrathin conformable form; reduce pain; highly occlusive property allows patient to continue daily activity; molds well to wound; some transparent forms allow visualization of wound; barrier versus bacteria and contaminants; can be left for 7 days</td>
<td>May leave residue or adhere to wound surfaces; not recommended with heavy exudate, active infection, or sinus tracts; contraindicated in third-degree burns; injury of periwound skin; highly occlusive property can promote anaerobic infection in certain patients; may promote hypertrophic granulation tissue; may leave residue and odor that can be mistaken for infection</td>
<td>Allevyn (Smith &amp; Nephew, London, United Kingdom); DuoDERM (Convatec, Skillman, N.J.); Hydrocol (Bertek, Rockford, Ill.); Invacare Hydrocolloid (Invacare Supply Group, Elyria, Ohio); Tegasorb (3M, St. Paul, Minn.)</td>
</tr>
<tr>
<td>Hydrogels</td>
<td>Glycerin- or water-based cross-linked polymer gels or sheet; up to 96% water-based, semipermeable, transmits vapor and water; amorphous gels, sheet dressings, or beads; secondary dressing can provide enhanced absorption and compression; bead type dressing can absorb microorganisms, exudate, or wound debris</td>
<td>Minimal</td>
<td>Minimal to moderate exudate in superficial to deep wounds; rehydration of wound bed; gel form can pack deep wounds and conform to wound defects; autolytic débridement, especially with necrotic, dry eschar; change daily to 7 days</td>
<td>Cooling effect of sheet hydrogels may provide relief in burned or excoriated wounds; can be used with infection</td>
<td>Minimal absorption; desiccates quickly without covering; excess use can cause wound maceration; may promote yeast; sheet dressing requires secondary securement</td>
<td>Amorphous types include Comfeel Triad (Coloplast, Minneapolis, Minn.), DuoDERM (Convatec, Skillman, N.J.), and Restore Hydrogel (Hollister, Libertyville, Ill.); Sheet types include AQUAFLO (Kendall, Dublin, Ireland), Aquate (Dermasciences, Princeton, N.J.), AQUASORB (DeRoyal, Powell, Tenn.), and Carradres (Carrington Laboratories, Irving, Texas)</td>
</tr>
</tbody>
</table>
| Contact layers/low adherent | Provides layer between dressing and wound bed to protect fragile healing tissue; single layer; reduces adherence of wound to dressing; woven or nonwoven | Scant            | Granulation tissue requiring some moisture; apply directly over the wound or over topical medication | Cheap; widely available | Exudates will soak through to above dressing, not to be used in viscous exudates or third-degree burns | Demanet Wound Contact Layer (DeRoyal, Powell, Tenn.); Mepitel Soft Silicone Wound Contact Layer (Mölnlycke Health Care, Göteborg, Sweden); Profore WCL (Smith & Nephew); ProGuide WCL (Smith & Nephew); 3M Tegasorb (3M, St. Paul, Minn.) | (Continued)
Depending on the type, occlusive dressings can also manage exudates (Table 1). Randomized trials have demonstrated increased speed and less painful healing in acute, superficial wounds compared with nonocclusive modalities. An increased rate of healing has been observed when dressings are placed within 2 hours of injury and kept on for at least 24 hours.

Theoretically, a moist environment provides a good environment for bacterial colonization and possibly infection, which can be an impediment to applying occlusion. This has not been shown to be true: occlusion actually provides a barrier against infection and reduces infection rates.

Although partial-thickness healing is faster under occlusion, it is less clear whether occlusive dressings speed acute, full-thickness wound healing. In the absence of wound site disease, full-thickness wounds will eventually heal by means of secondary intention. Although some experimental data in pigs suggest complete healing is faster with occlusive dressings in full-thickness wounds versus nonocclusive therapy, the speed at which epithelialization occurs and concomitant contractures are often not optimal or desirable in patients. Most clinicians will opt for grafts or flaps instead.

Similarly, the effect of occlusion on chronic wounds has not been fully elucidated, as evidence is mixed. It has been demonstrated that chronic wound fluid under occlusive dressings actually inhibit cell proliferation in vitro by restricting entry into the S phase and DNA production, and degradation of adhesion proteins.

Despite this, there are many reasons to justify the use of occlusion in chronic wounds. It has been shown to facilitate painless and effective autolytic débridement, which is the use of enzymes within the wound fluid to remove necrotic debris. Occlusion reduces cost because of less frequent dressing changes compared with standard gauze. Furthermore, the same principles of pain reduction, exudate management, and safety with the use of occlusive dressings apply in the chronic wound.

Currently, dressing modalities are chosen mostly based on opinion, as high-level evidence is conflicting. Although some meta-analyses have demonstrated benefits of occlusive dressings in the treatment of pressure ulcers and chronic wounds, other authors have found insufficient evidence to recommend modern dressings for pressure ulcers, arterial leg ulcers, chronic leg ulcers, venous ulcers, or surgical wounds healing by secondary intention. The lack of effective animal models available for study and

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
<th>Indications</th>
<th>Advantage</th>
<th>Disadvantage</th>
<th>Examples of Available Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composites</td>
<td>Two or more distinct dressings combined to take advantage of each different absorptive layer, adhesive border, and nonadherent layer for wound covering</td>
<td>IV: intravenous.</td>
<td>Wound Care 3rd ed. Philadelphia: Lippincott Williams &amp; Wilkins; 2005; and Jones V, Grey JE, Harding KG. Wound dressings. BMJ 2006;332:777–780.</td>
<td></td>
<td>Aquacel Hydrofiber (ConvaTec, Skillman, N.J.); Comfeel Plus (Coloplast, Minneapolis, Minn.); CovaDerm (DeRoyal, Powell, Tenn.); Tegaderm, Tegaderm Foam (3M); Tegaderm Hydrocolloid (3M); Tegaderm with Absorbent Pad (3M).</td>
</tr>
</tbody>
</table>
level I evidence making providing evidence-based recommendations difficult.29,30,32,66

Awaiting better evidence, dressing choices should be based on clinical experience.70,71 Ease of use, patient preference, amount of wound drainage, and protection against bacteria should all be taken into consideration (Table 1).30,64,72 A moist yet absorbent environment needs to be maintained, avoiding wound maceration or dehydration.30,70,71,73,74 Dressings should minimize external forces such as friction and shear and should stay in place.70,71 Fear of maceration and its potential complications in certain wound types suggest completely occlusive and highly adhesive dressings should be avoided in diabetic foot ulcer,75 and hydrogels should be used instead.65

**Active Dressings**

Interest in development of active dressings stems from the altered biology of the chronic wound (Table 2).27,34,58,77 Potential targets include increased bacterial load and excessive protease levels, which lead to the development of antimicrobial, protease inhibitor,76 and collagen dressings.21 The combination of antimicrobials with the dressings described above affords bacterial reduction and maintains a moist environment.

**Collagen Dressings**

Collagen has long been known to have a critical function in wound healing, providing platelet aggregation; hemostasis; and chemotaxis of macrophages, granulocytes, and fibroblasts.78 It was rationalized that exogenous collagen matrices might provide a scaffold for tissue ingrowth when endogenous collagen is disrupted by the proteolytic wound environment.21 In addition, dressings containing oxidized regenerated cellulose bind the high level of proteases seen in chronic wounds, protecting growth factors from destruction and neutralizing free radical damage.79,80

However, randomized controlled trials of 55 percent bovine collagen to 44 percent oxidized regenerated cellulose dressing (Promogran wound matrix; Systagenix, Commonwealth, Mass.) did not demonstrate significantly better wound closure of Wagner grade I or II diabetic foot ulcers83 or venous leg ulcers,82 although variability of loading (for the former study) and dressing change procedure might have negatively affected these results.

Another collagen dressing comprised of porcine-derived acellular small intestine submucosa (Oasis Wound Matrix, Fort Worth, Texas) was found to be equivalent to recombinant human platelet-derived growth factor (rhPDGF)-BB in diabetic ulcers (see below) (becaplermin, Regranex; Systagenix, Commonwealth, Mass.).85 The dressing was found to improve healing in full-thickness diabetic ulcers84 and mixed vascular ulcers85 when compared with standard-of-care treatment at 12 weeks and petroleum gauze at 8 weeks, respectively.

**TOPICAL ANTIMICROBIALS**

The ideal antimicrobial exists in an equilibrium whereby bacteria bioburden is reduced without interfering with cellular processes by means of cytotoxicities.16,20,86 Although antibiotics have specific sites of activity, antimicrobials have a lower incidence of resistance and multiple sites of activity, and target a wide variety of bacteria, protozoa, fungi, viruses, and prions.16,20,87 The most commonly used products include chlorhexidine, povidone-iodine, cadexomer iodine, alcohol, acetate, hydrogen peroxide, boric acid, silver sulfadiazine (an antibiotic), silver nitrate, and sodium hypochlorite (Table 3).26,45,88–106

Iodophors, a class of antiseptic including povidone-iodine and cadexomer iodine, are slow-release carriers designed to curb elemental iodine toxicity.87 Most in vitro studies suggest that povidone-iodine is toxic to the cells that participate in wound healing. In vivo studies have not found that it promotes good wound healing.91,107 However, evidence exists suggesting cadexomer iodine, compared with standard-of-care regimens, results in significantly higher complete venous ulcer healing rates.96 It is also more cost effective, results in less infection, and has fewer adverse effects than hydrocolloids or paraffin gauze.97

Silver compounds, particularly silver nitrate and silver sulfadiazine, have been used widely in burns. The reactivity of silver compounds with negative substances such as DNA, RNA, proteins, and components of the electron transport system is the heart of its antimicrobial effect.87 Such reactivity requires a carrier for consistent slow delivery to balance the cellular toxicity against the microbicidal activity.

Moyer et al. found that 0.5% silver nitrate administered on gauze dressing achieved such balance.102,108 However, silver nitrate darkens tissue, causes hyponatremia and hypochloremia, and has been shown to be systemically absorbed.103 The very frequent applications, up to 12 times per day, results in a large excess of silver at the wound site.109 Furthermore, nitrate is converted to nitrite, an oxidant capable of cell damage.

The advent of silver sulfadiazine, created from the combination of silver nitrate and sodium sulfadiazine, allowed for better delivery of silver, allowing...
Table 2. Available Active Dressing Types*

<table>
<thead>
<tr>
<th>Type</th>
<th>Indications</th>
<th>Comment</th>
<th>Commercial Available Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antimicrobial dressings</td>
<td>Moderate to heavy exudate depending on the passive dressing; may be primary or secondary depending on the dressing chosen</td>
<td>Silver-releasing foam shown to decrease ulcer area, odor, leakages, and maceration; no significance in terms of achieving complete wound healing; greater reduction in chronic, infected, ulcer size with silver-containing foam dressings compared with standard foam or best local practice after 4 wk</td>
<td>Acticoat (Smith &amp; Nephew, London, United Kingdom); Algicell Ag (Dermasciences, Princeton, N.J.); Aquacel Ag (ConvaTec, Skillman, N.J.); Contreet Foam/Biatain–Ag (Coloplast, Minneapolis, Minn.); Contreet Hydrocolloid/Confed Ag (Coloplast); Invacare Silver Alginate (Invacare Supply Group, Elyria, Ohio); Iodosorb Gel and Iodoxlex Pad (Healthpoint, Fort Worth, Texas); Maxorb Extra (Medline, Mundelein, Ill.); ReliaMed Silver Alginate (ReliaMed, Fort Worth, Texas); Restore Foam with Silver (Hollister, Libertyville, Ill.); Silvasorb (Medline, Mundelein, Ill.); Silvercel (Johnson &amp; Johnson, New Brunswick, N.J.); Silverlon (Silverlon Consumer Products, Geneva, Ill.)</td>
</tr>
<tr>
<td>Collagen dressings</td>
<td>Moderate to heavy exudate in superficial to deep wounds; can be used in infected wounds; can be used in skin grafts, donor sites, red or yellow wounds</td>
<td>Provides a scaffold for growth of tissue; hydrophilic nature allows cell attachment; collagen encourages hemostasis; chemotactic to fibroblasts, granulocytes, macrophages; oxidized regenerated cellulose inactivates excess protease and protects growth factors</td>
<td>55% bovine collagen and 45% oxidized regenerated cellulose (Promogran wound matrix; Systagenix, North Yorkshire, United Kingdom); 90% bovine collagen and 10% alginate (Fibracol plus collagen dressing with alginate; Systagenix); 100% bovine collagen (Medifill; Human BioSciences, Gaithersburg, Md.); 100% porcine collagen (Oasis, Cook Biotech, Fort Worth, Texas); collagen with sodium alginate (Colactive; Smith &amp; Nephew, London, United Kingdom); type 1 hydrolyzed bovine collagen (GellerateRX; Wound Care Innovations, Fort Lauderdale, Fla.)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type</th>
<th>Composition</th>
<th>Indications</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Povidone-iodine</td>
<td>Iodophor; complex of polyvinyl/pyrrolidone and 1–10% iodine; available as a solution, cream, scrub, ointment</td>
<td>Approved for short-term treatment of superficial and acute wounds</td>
<td>FDA has concluded no evidence of improved or slowed wound healing&lt;sup&gt;89&lt;/sup&gt;; irrigation with povidone-iodine in 12-hr-old wounds colonized by &lt;i&gt;Staphylococcus aureus&lt;/i&gt; in guinea pigs showed no significant decrease in bacterial count&lt;sup&gt;89&lt;/sup&gt;; 1% povidone-iodine decreased wound infection in surgical wounds, whereas 5% povidone-iodine aerosol inhibited leukocyte migration and resulted in increased infection&lt;sup&gt;26&lt;/sup&gt;; 1% povidone-iodine was nonsignificant in decreasing bacterial counts vs. normal saline in acute traumatic wounds after 10-min soak&lt;sup&gt;91&lt;/sup&gt;; 1% povidone-iodine no more effective than saline in chronic pressure ulcers&lt;sup&gt;92&lt;/sup&gt;; no effect on wound healing in 1% formulations&lt;sup&gt;26&lt;/sup&gt;; no resistance has been demonstrated&lt;sup&gt;93&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cadexomer iodine</td>
<td>Iodophor; microspheres 0.1–0.3 mm in diameter in a cadexomer-starch with iodine physically fixed within the sphere; iodine performs its antimicrobial activity as bacteria and exudates are absorbed within the sphere&lt;sup&gt;45&lt;/sup&gt;; available as ointment or cream</td>
<td>Short-term use in healable, superficial wounds with high bacterial burden&lt;sup&gt;94&lt;/sup&gt;; silver dressings, silver sulfadiazine, and cadexomer effective against MRSA&lt;sup&gt;95&lt;/sup&gt;</td>
<td>Found to generate higher rates of complete healing at 4–6 wk vs. control when all patients receive standard of care in venous leg ulcers&lt;sup&gt;96&lt;/sup&gt;; cadexomer iodine paste more cost effective vs. hydrocolloid or paraffin dressings in venous ulcers with compression therapy&lt;sup&gt;97&lt;/sup&gt;; increased epidermal regeneration in full-thickness wounds compared with cadexomer-starch ointment or saline treatment,&lt;sup&gt;98&lt;/sup&gt; and partial-thickness wounds&lt;sup&gt;97&lt;/sup&gt;; avoid use in in patients with thyroid abnormalities&lt;sup&gt;98&lt;/sup&gt;; good absorptive properties; 1 g of cadexomer can absorb 7 ml of liquid&lt;sup&gt;35&lt;/sup&gt;</td>
</tr>
<tr>
<td>Hydrogen peroxide</td>
<td>3% hydrogen peroxide is most common; 6% in some medical formulations</td>
<td>Effective debrider by loosening necrotic debris&lt;sup&gt;88&lt;/sup&gt;</td>
<td>No statistical difference in wound infection rates in surgical wounds in 3% hydrogen peroxide vs. control&lt;sup&gt;99&lt;/sup&gt;; may cause tissue embolism in open wounds&lt;sup&gt;99&lt;/sup&gt;; gas-producing property may cause oxygen bubbles in newly formed skin&lt;sup&gt;100&lt;/sup&gt;</td>
</tr>
<tr>
<td>Acetic acid</td>
<td>0.5–1% acetic acid (white vinegar)</td>
<td>Decreases pH to inhibit &lt;i&gt;Pseudomonas&lt;/i&gt; growth</td>
<td>Possible cytotoxicity&lt;sup&gt;101&lt;/sup&gt; although other studies have shown no effect on the wound healing environment in vitro&lt;sup&gt;100&lt;/sup&gt;; Persistent activity within the stratum corneum&lt;sup&gt;100&lt;/sup&gt;; no definitive evidence of cytotoxicity&lt;sup&gt;88&lt;/sup&gt;; not enough evidence to draw conclusion regarding chlorhexidine use in open wounds&lt;sup&gt;98&lt;/sup&gt;</td>
</tr>
<tr>
<td>Chlorhexidine</td>
<td>Available in 0.5–4.0%</td>
<td>Surgical irrigation, wash hand</td>
<td></td>
</tr>
<tr>
<td>Silver compounds</td>
<td>Silver nitrate; silver sulfadiazine (antibiotic); silver charcoal; nanocrystalline silver-sustained silver-releasing systems (dressings); silver calcium sodium carboxymethylcellulose dressing</td>
<td>Silver sulfadiazine is commonly used as a topical burn wound treatment; silver dressings, silver sulfadiazine, and cadexomer effective against MRSA&lt;sup&gt;85&lt;/sup&gt;</td>
<td>Silver nitrate stains objects on contact, causes hypochloremia and hyponatremia, and is deposited within kidney, spleen, liver, and muscles&lt;sup&gt;102,103&lt;/sup&gt;; delay in healing of superficial and partial-thickness burn wounds treated with silver sulfadiazine for the full duration of treatment&lt;sup&gt;104,105&lt;/sup&gt;; slow emergence of silver-resistant bacteria with prolonged use&lt;sup&gt;106&lt;/sup&gt;; silver sulfadiazine rarely causes temporary leukopenia&lt;sup&gt;102&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

FDA, U.S. Food and Drug Administration; MRSA, methicillin-resistant <i>Staphylococcus aureus</i>.  
application two times per day. Fox demonstrated the elimination of *Pseudomonas* in burn wounds, and reduction in mortality and destruction in muscle and skin compared with silver nitrate and mafenide acetate.\(^{110,111}\) Since then, silver sulfadiazine gauze has been used widely as an antibiotic in the topical treatment of second- to third-degree burns. Nanocrystalline silver dressings represent further modification in prolongation of silver delivery.\(^{109}\) With sustained release of silver in a less rapidly deactivated form, daily or weekly dressing change with steady silver release can be achieved.

Despite large bodies of research on the benefits of silver therapeutics, much less evidence regarding the effect of silver ion on the wound bed exists.\(^{109}\) In vitro, silver has been shown to delay wound healing when compared with tulle gras dressing by means of toxicity to keratinocytes and fibroblasts.\(^{112}\) In vivo, a similar delay in healing exists with partial-thickness burns treated with silver sulfadiazine.\(^{113}\) Two recent Cochrane reports found little evidence to support use of silver sulfadiazine in burn wounds or silver-containing dressing in wounds because of a lack of clinical proof of wound infection prevention or increased rate of healing.\(^{104,105}\)

As with occlusive dressings, a lack of high-quality evidence exists.\(^{68,114,115}\) Recommendations are often based on expert opinion or personal preference.\(^{94}\) Topical antiseptics should be reserved for signs of bacterial burden detrimental to healing as evidenced by clinical signs (described above) or by failure to heal to avoid possible cytotoxicity.\(^{20,21,109}\)

### GROWTH FACTORS

In a series of elegant experiments, Cohen noticed that the purification of submaxillary gland extracts led to earlier eyelid separation and eruption of the incisor in mice, which eventually led to the isolation of the first growth factor, epidermal growth factor, and the 1986 Nobel Prize in Medicine.\(^{116}\) Since Cohen’s discovery, knowledge of growth factors has increased. In the acute wound, growth factors function in a paracrine, autocrine, intercrine, or endocrine manner, stimulating healing.\(^{15}\) However, in the chronic wound, the balance between stimulation and inhibition is lost, as growth factors and their receptors are destroyed,\(^{15,117}\) trapped,\(^{118}\) or maldistributed in the chronic wound. Fibroblasts have also been reported to be less responsive to growth hormone, likely secondary to senescence.\(^{119}\)

#### Platelet-Derived Growth Factor

Currently, rhPDGF-BB is the only growth factor approved by the U.S. Food and Drug Administration for use in chronic wounds (Table 4).\(^{121–123}\) Becaplermin is rhPDGF-BB produced by the yeast *Saccharomyces cerevisiae*. The BB isoform is the only one of the three (PDGF-AA, PDGF-AB, and PDGF-BB) that has been shown to bind to both alpha and beta receptors.\(^{120}\) Prepared as a topical gel, becaplermin has been approved for the treatment of lower extremity diabetic neuropathic ulcers that extend into the subcutaneous tissue or beyond and have an adequate blood supply (stage III or IV).

A meta-analysis of 922 patients among four trials of rhPDGF-BB in full-thickness, nonhealing, lower extremity diabetic ulcers found that becaplermin with good wound care leads to a significant increase in complete healing when compared with placebo.\(^{121}\) Among the studies included in the meta-analysis, Steed found that patients \((n = 118)\) treated with rhPDGF-BB compared with placebo achieved significantly higher complete wound healing rates when evaluated at 20 weeks. Although not statistically significant, there was a greater recurrence rate in placebo (46 percent) compared with rhPDGF-BB (26 percent).\(^{121}\) This trial was the first to demonstrate that topical application of a single growth factor could speed healing of a chronic wound. In a pivotal trial, Wieman et al. found that patients \((n = 382)\) treated with 100 µg/g of becaplermin gel experienced significantly increased complete diabetic lower extremity ulcer closure compared with placebo-treated patients.\(^{125}\)

Despite the impressive findings, becaplermin has recently received a new black box warning from the U.S. Food and Drug Administration. Although no increase in incidence of cancer was found, there was an increased mortality secondary to malignancy in those using three or more tubes.\(^{122}\) The U.S. Food and Drug Administration does not recommend becaplermin for those with known malignancies. However, longer follow-up of those patients in the original report found that the increase in mortality among the becaplermin-treated group did not persist.\(^{126}\)

Epidermal growth factor and macrophage colony-stimulating factor are being examined for use in wound healing.\(^{127,128}\) Although initial results were promising, fibroblast growth factor-2 has had its production discontinued.\(^{129}\)

#### ENGINEERED LIVING SKIN

Despite use of standard of care and advanced topical treatments, some wounds fail to improve.\(^{130}\)
Another topical therapy, engineered skin, is an option (Table 5). Engineered skin was initially envisioned to treat burn wounds when autologous grafts were unavailable. Engineered skin was initially envisioned to treat burn wounds when autologous grafts were unavailable. However, skin substitutes have received wider applications in chronic venous and diabetic wounds, stimulating healing through a variety of potential mechanisms. Two major classes of cellular engineered skin are currently used in the United States: dermal and bilayered constructs.

### Cellular Dermal Constructs

As a living dermal substitute, human fibroblast–derived dermal substitute is created by seeding fibroblasts derived from neonatal foreskin onto a bioabsorbable polylactin matrix (Dermagraft; Advanced BioHealing, Inc., La Jolla, Calif.). The fibroblasts secrete adhesion molecules and growth factors as epithelialization occurs over the dermal bed replacement. Dermagraft was found to result in a faster and higher percentage of complete healing in full-thickness, chronic (>6 weeks) diabetic ulcers compared with conventional therapy.

### Bilayered Constructs

The bilayered construct is composed of living keratinocytes for epidermis and fibroblasts derived from neonatal foreskin, placed within a bovine type I collagen matrix for dermis. Apligraf (Organogenesis, Canton, Mass.) is designed to resemble skin, with cells producing a milieu of growth factors, collagen, and extracellular matrix proteins to promote reepithelialization, granulation tissue formation, and angiogenesis, while providing protection against infection. In randomized controlled trials, Apligraf achieved a significantly faster and higher rate of complete healing in venous ulcers and diabetic foot ulcers, with lower incidences of osteomyelitis and amputations in the latter disease compared with the standard of care.

### ENGINEERED ACELLULAR SKIN: ACCELULAR DERMAL SUBSTITUTES

In addition to cellular constructs, acellular constructs have been developed primarily for burn wounds. One such product is AlloDerm (LifeCell Corp., Branchburg, N.J.), a cadaveric skin processed to remove cellular and antigenic components, leaving an acellular dermal matrix with an intact basement membrane complex. It has seen use in burns, abdominal wall reconstruction, and breast reconstruction, to name a few.
<table>
<thead>
<tr>
<th>Type</th>
<th>FDA Indications</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermal replacement</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Human cryopreserved allograft skin</td>
<td>Temporary coverage for burns until permanent coverage; supplied by tissue banks</td>
<td>Long use has provided much experience</td>
<td>Limited supply; disease transmission; sloughing/rejection by 2 wk; difficult to remove off of wound bed; performance with cryopreservation</td>
</tr>
<tr>
<td>Bioabsorbable membrane impregnated with human dermal fibroblasts from neonatal foreskin (Dermagraft, Advanced BioHealing, Inc., La Jolla, Calif.)</td>
<td>FDA approval for Dermagraft in full-thickness diabetic foot ulcers that have been present for longer than 6 wk and ulcers that extend deeper into the skin where the blood vessels are, but do not involve tendon, muscle, joint capsule, or bone (PMA/2001); FDA approval for Dermagraft for ulcers secondary to epidermolysis bullosa (HDE/2004)</td>
<td>Dermagraft allows the patient’s own epithelial cells to close the wound; biodegradable matrix allows absorption in 3–4 wk; lower number of wound infections, osteomyelitis, and cellulitis and fewer surgical procedures involving the diabetic foot ulcer</td>
<td>Short shelf life unless cryopreserved; contraindicated in ulcers with infections, sinus tracts, or in patients with bovine product hypersensitivity</td>
</tr>
<tr>
<td>Human allograft skin chemically treated for decellularization, freeze-dried for moisture removal, and stabilization of dermal matrix (AlloDerm, LifeCell Corp., Branchburg, N.J.)</td>
<td>Burns, abdominal wall repairs, breast reconstruction, nasal septum reconstruction, tympanic membrane grafting</td>
<td></td>
<td>Low risk of disease transmission; contraindicated in infected or nonvascular wounds; cost</td>
</tr>
<tr>
<td>Polymer of bovine collagen type 1 collagen and shark chondroitin-6-sulfate with an overlying silastic sheet (Integra; Integra LifeSciences Corp., Plainsboro, N.J.)</td>
<td>Postexcisional treatment of life-threatening full-thickness or deep partial-thickness thermal injury where sufficient autograft is not available (PMA/1996); patients undergoing reconstructive surgery for burn scar contracture where there is a limited amount of their own skin to use for autografts or they are too ill to have more wound sites created (2002)</td>
<td>Immediate wound coverage; allows ultrathin split-thickness autograft; better cosmetic outcome versus split-thickness autograft; histologic analysis shows good wound healing with minimal scarring; immunologically well tolerated; silicone is transparent, allowing visualization</td>
<td>Complete wound excision before grafting; study performed within 7 days; learning curve of 10 procedures; contraindications include known hypersensitivity to ingredients and patients with hemochromatosis, hemosiderosis, hemolytic anemias, and pernicious anemia; cost</td>
</tr>
<tr>
<td>Bilayered substitute</td>
<td>Noninfected partial- and full-thickness skin ulcers secondary to venous insufficiency &gt;1 mo duration that have not responded to conventional treatment (PMA/1998); full-thickness neuropathic diabetic foot ulcers that have extended into the dermis but not with tendon, muscle, capsule, or bone exposure, of greater than 3-wk duration, that have not adequately responded to conventional ulcer therapy (PMA/1998)</td>
<td>Immediate availability; self-heal when injured; no clinical evidence of rejection, sensitization, or immunogenicity; does not contain blood vessels, sweat glands, hair follicles, macrophages, Langerhans cells, lymphocytes, melanocytes; no difference in wound infection, cellulitis, or pain in venous ulcer treatment; contains stratum corneum to prevent desicication; benefit in large, deep, and chronic venous ulcers</td>
<td>10-day shelf life; studies performed an average of 3.9 applications for diabetic ulcers and 3.34 applications for venous ulcers; learning curve correlates with outcome; contraindications include patients with known bovine collagen allergies or who have infected wounds</td>
</tr>
</tbody>
</table>

FDA, U.S. Food and Drug Administration; PMA, premarket approval; HDE, Humanitarian Device Exemption; 510K, device provides similar efficacy and safety to the device it replaces.

Another approach is to use acellular bovine collagen matrices with shark-derived chondroitin sulfate matrices bonded to a temporary Silastic epidermis (Integra: Integra LifeSciences Corp., Plainsboro, N.J.). Along with serving as a conduit for growth factors and angiogenesis, these acellular matrices serve as a transient biodegradable scaffold as a new dermis is regenerated. Integra provides temporary covering when immediate grafting is not possible. Studies have shown that Integra has similar graft take compared with non-autograft controls in wounds with a large body surface area, but with better patient satisfaction, less hypertrophic scarring, and shorter hospital stays. Moiemen et al. demonstrated Integra’s use in reconstructive surgery, especially in contracture and scar repair, with patients reporting improvement in range of motion, softness, and appearance.

CONCLUSIONS

Wound healing has evolved much over the past 40 years. Many therapies have been devised to interrupt the vicious cycle of nonhealing wounds. Exciting developments in the field of wound healing include the use of growth factors and skin substitutes. Studies demonstrate the benefits of the aforementioned treatments, many of the modalities used in practice today, such as dressings and antimicrobials, are based more on clinical experience than evidence. High-quality studies are lacking to evaluate such therapies. Proof of patient benefit will provide the necessary justification for use in clinical practice.

Robert S. Kirsner, M.D., Ph.D.
Department of Dermatology and Cutaneous Surgery
University of Miami Miller School of Medicine
1600 N.W. 10th Avenue
Rosenstiel Medical Science Building, Room 2023-A
Miami, Fla. 33136
rkkirsner@med.miami.edu

REFERENCES


130. Li W. Personal communication, 2008.


Volume 127, Number 1S • Topical Wound Healing


