

# Management of pressure ulcers

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A pressure ulcer is defined as a wound caused by incessant pressure or repeated friction that damages the skin and its underlying architecture. This condition has also been referred to as a bedsore, decubitus ulcer, or pressure sore. Interest in the management of pressure ulcers, once primarily a focus of nurses,<sup>1</sup> has expanded in the past 10 years. The increased focus on this condition may be attributable to the aging of the population, growing residency in long-term-care facilities, rising health care costs, and advances in treatment. One study reported that the cost of prevention and treatment was \$167 to \$245 per ulcer.<sup>2</sup> A more recent clinical trial reported that the cost of materials needed to treat a pressure ulcer ranged from \$112 to more than \$6,000.<sup>3</sup> Given that the total cost of healing a pressure ulcer ranges from \$2,000 to \$70,000,<sup>4</sup> identifying optimal prevention and management strategies is likely to remain a priority of health care.

This article discusses skin function and structure, the process of wound healing, the epidemiology and staging of pressure ulcers, and pressure ulcer prevention and treatment.

**Purpose.** Wound healing, the epidemiology and staging of pressure ulcers, and pressure ulcer prevention and treatment are discussed.

**Summary.** The principal event leading to the formation of pressure ulcers appears to be a consistent interruption in blood supply to the skin. Several known risk factors exist and can be attributed to patient-specific variables and wound-specific conditions. Initial management should include removal of the source of pressure, a comprehensive assessment of the patient, and proper staging of the ulcer. Preparation of the wound for treatment is essential and can have a significant impact on healing. While the patient's nutritional status is thought to affect wound healing, only an increased protein content in the diet has been demonstrated to have a benefit. Specialized wound dressings are available for pressure ulcers of all stages and drainage characteristics. With wide variation in cost and in application regimens, a direct cost-effectiveness comparison of commercially available dressing products is difficult. Many of the growth

factors commonly present in healing wounds have been synthesized and evaluated as treatments. Although topical platelet-derived growth factor has demonstrated benefit in some studies, its use remains controversial. To date, no topical growth factors carry FDA-approved labeling for use in the treatment of pressure ulcers. Human skin equivalents mark the latest advancement in therapy. Certain species of bacteria have been associated with poorly healing ulcers and may warrant intervention with either local or systemic antibiotic therapy.

**Conclusion.** No pharmacologic intervention has been conclusively shown to be effective for pressure ulcers. The cornerstones of therapy remain elimination of the source of pressure or friction and appropriate wound care.

**Index terms:** Antiinfective agents; Decubitus ulcer; Dressings; Economics; Epidemiology; Growth factors; Nutrition; Wound healing

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## Skin function and structure

The skin varies in thickness from less than 1 mm (the eardrum) to 6 mm (covering the palms of the hands and the soles of the feet).<sup>5</sup> Thermoregulation and protection from

exposure to bacteria, chemicals, and harmful radiation are the skin's more important roles. This boundary separating the human body from the environment is reinforced by a variety of macrophage and mast cells that

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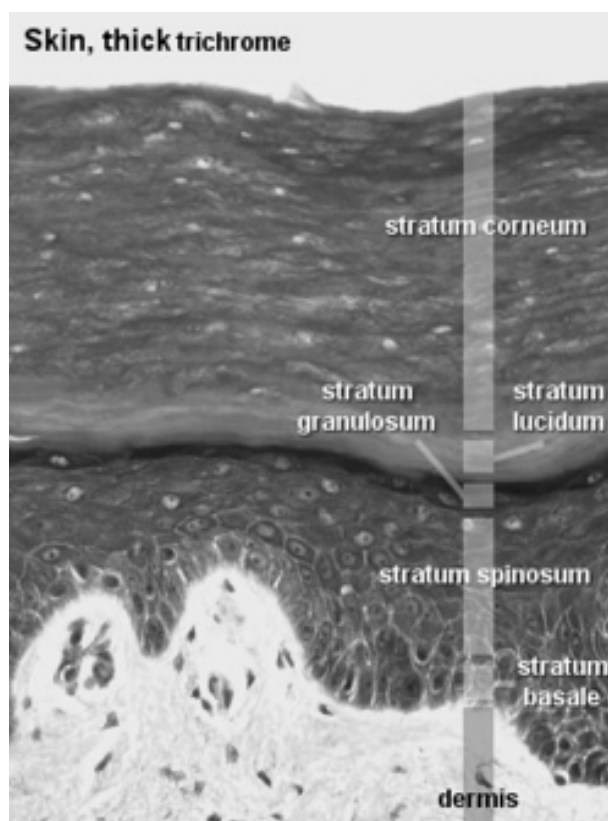
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destroy pathogens and mediate the inflammatory response.<sup>5</sup> Thermoregulation is accomplished primarily by the presence or absence of hair, alterations in the circulation to the skin via dermal blood vessels, and sweating. The skin also incorporates an intricate array of nerves and receptors that allow humans to perceive pain, pressure, temperature, and touch. Finally, the skin synthesizes vitamin D by converting 7-dehydrocholesterol to cholecalciferol.<sup>6</sup>

The skin consists of three major layers: the epidermis, the outermost layer, which protects against infection and dehydration, among other functions; the dermis, a layer of connective tissue containing nerves, blood vessels, and lymphatics; and the subcutaneous layer, which contains adipose tissue. The epidermis has several layers, contains no vasculature, and relies on the dermis for oxygenation.<sup>7</sup> The outermost layer of the epidermis is the stratum corneum, containing dead, keratin-filled cells (Figure 1). This layer provides protection from chemical, physical, and thermal exposure and is shed continuously through contact with the environment. The stratum corneum is regenerated by the underlying epidermal layers. Usually, the stratum lucidum is present only in the thicker skin layers. The cells migrating through this layer are exposed to a variety of enzymatic processes and lose their nuclei and organelles.<sup>8</sup> The cells that make up the stratum granulosum still possess nuclei and are further distinguished from the other layers by the presence of profilaggrin, a precursor of the protein that facilitates keratin assembly.<sup>7</sup>

The cells in the stratum spinosum contain desmosomes and produce substrates for the production of cornified envelopes. The innermost layer of the epidermis, the stratum basale, gives rise to all the outer layers. A host of migrating cells are present there, including melano-

Figure 1. Photomicrograph of cross-section of skin.



cytes, the cells that produce melanin; Merkel cells, which are thought to function as touch receptors<sup>6</sup>; and Langerhans cells, which play a key role in the recognition and presentation of antigens.

The basement membrane is an acellular, semipermeable layer that controls the amount and composition of materials that pass between the epidermis and the dermis. An assortment of proteins are found in this layer, including collagen, fibronectin, and heparin sulfate proteoglycan.<sup>8</sup>

The dermis is composed largely of fibroblast cells and is vascular and innervated. The principal structural proteins in this layer are collagen, elastin, fibronectin, and various proteoglycans. Each protein plays an integral role in skin metabolism, healing, strength, and resiliency. This layer provides the skin with volume and serves as an attachment for the other skin layers.

### Wound healing

Although the skin is designed to be worn off and replaced, skin repair and regeneration are complex. After hemostasis is achieved at the site of injury, degranulating platelets at the site initiate an inflammatory response and attract neutrophils to the area. This marks the beginning of the inflammation phase, lasting two to three days.<sup>9</sup> Epidermal growth factor (EGF), insulin-like growth factor-I (IGF-I), platelet-derived growth factor (PDGF), and transforming growth factor- $\beta$  (TGF- $\beta$ ) are released. TGF- $\beta$  and fibroblast cells, along with tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) from damaged blood vessels in the area, attract inflammatory cells to the wound site.<sup>9</sup>

Neutrophils and macrophages are prevalent in the early part of the inflammation phase. In addition to synthesizing additional growth and inflammatory factors, these cells play

a central role in the removal of the preexisting tissue matrix, nonviable tissue, pathogens, and extraneous material at the wound site. As the neutrophils diminish, macrophages continue to produce additional growth factors, such as basic fibroblast growth factor (bFGF), leukocyte-derived growth factor, interleukin-1 (IL-1), and interleukin-6 (IL-6). These factors attract additional cells necessary for reconstruction of the injured tissue, resulting in the formation of a provisional, or temporary, matrix.<sup>9</sup> Macrophages also release proteases to break down collagen, elastin, and nitric oxide; the latter destroys bacteria and inhibits DNA virus replication.<sup>10</sup>

The proliferation phase is characterized by the formation of a stable extracellular matrix, or granulation tissue. This phase lasts several days to weeks. As the macrophages dwindle, endothelial cells, fibroblasts, and keratinocytes emerge. They produce additional growth factors that stimulate production of the collagen-rich matrix and new blood vessels. As this new matrix is forming, the provisional matrix is broken down by a number of enzyme systems. Regulation of the degradation enzymes is thought to be controlled by tissue inhibitors.<sup>11</sup> The wound begins to contract and eventually closes.

The remodeling phase begins when the wound has closed and is distinguished by changes in both the cellular content and the blood supply to the resulting tissue. This process may continue for many months to years.<sup>12</sup> The tissue undergoes extensive remodeling as collagen and elastin are added and degraded by fibroblasts. Ultimately, the scar tissue ceases to produce new components, and, although the new tissue is structurally inferior to undamaged tissue, the process of healing is complete.

### Epidemiology

Pressure ulcers are a type of chronic wound, differing in many re-

spects from acute wounds. In most cases, acute wounds undergo a chronological progression through the healing cycle, contain a nominal bacterial load, and result in a minimal loss of tissue, with little scarring. In contrast, chronic wounds undergo all healing phases concurrently, frequently possess sizable bacterial contamination, and result in significant tissue damage and scarring.<sup>5</sup>

Pressure ulcers usually occur on the lower part of the body, predominantly the sacral region and heels. Among 3000 patients with pressure ulcers treated at 177 hospitals throughout the United States, 36% of all ulcers were located at the sacrum, closely followed in frequency by the heels (30%).<sup>13</sup> Other sites included the elbows (9%), ankles (7%), trochanters (6%), ischia (6%), knees (3%), scapulas (2%), shoulders (1%), and occiput (1%).

### Risk factors

Risk factors for the development of pressure ulcers may be loosely grouped into intrinsic and extrinsic factors. Patients have a variety of intrinsic variables that require consideration. Age appears to be one: Patients older than 75 years seem to be at the greatest risk, possibly because of age-related changes in the skin.<sup>14</sup> Patients who have limited mobility are also at increased risk. Conditions resulting in the loss of sensation or the perception of pain, such as diabetes and spinal cord injury, add to the risk. Another intrinsic factor is lack of consciousness or a limited sense of awareness. Loss of bowel or bladder control provides a source of both moisture and bacterial contamination that can promote the breakdown of skin. Poor nutritional status compounds the problem in patients who are unable to meet the increased metabolic demands of wound healing.

Extrinsic factors associated with pressure ulcers are derived from the environment surrounding the potential wound site. Pressure is the most

important extrinsic factor. The normal capillary filling pressure is 32 mm Hg; patients who are seated or bedridden for extended periods far exceed this value, and ulcer formation may begin.<sup>15</sup> Friction and shearing forces are extrinsic factors that enhance the loss of the stratum corneum by physical removal. Frictional forces act to pull on the skin while the weight of the body moves in the opposite direction. This may occur as a patient is repositioned in bed or transferred from bed to a wheelchair. Shearing forces are exerted when gravity causes the body to slide while in a fixed position. Patients elevated at an angle of 30° or more are particularly susceptible to this force.

### Etiology

Although the exact etiology of pressure ulcers is unclear, it is proposed that unrelenting pressure and repeated exposure to shearing forces are the initiating events. This hypothesis is supported by studies in surgical and nursing-home patients.<sup>16,17</sup> The underlying tissues are more predisposed to suffer injury from an interruption in blood flow than the epidermis.<sup>18</sup> Thus, the visual appearance of the ulcer may belie the full extent of the damage. Recently, pressure ulcers have been categorized as a type of ischemia-reperfusion injury.<sup>10</sup>

The causes of delayed healing of pressure ulcers are multifactorial. As with many chronic wounds, the constant presence of an eschar, pathogens, or foreign material impairs healing. Thus, removal of the source of the injury and all nonviable tissue and extraneous matter in the wound is considered essential to promoting healing. In some chronic wounds, decreased levels of PDGF, bFGF, and TGF- $\beta$  have been noted. However, these observations have not been reproduced in pressure ulcers.<sup>19</sup>

### Staging

According to the National Pres-

sure Ulcer Advisory Panel, pressure ulcers can be staged in one of four categories.<sup>20</sup> Stage 1 includes pressure ulcers with an observable pressure-related alteration of intact skin. Indicators may include skin temperature (warmth or coolness of the area relative to an adjacent or contralateral area), tissue consistency (either a firm or boggy feel), and sensation (pain, itching). Furthermore, the ulcer appears as a defined area of persistent redness in lightly pigmented skin or as persistent red, blue, or purple hues in more heavily pigmented skin. Stage 2 ulcers show partial-thickness skin loss involving the epidermis, the dermis, or both. The ulcer is superficial and appears clinically as an abrasion, blister, or shallow crater. Stage 3 includes pressure ulcers with full-thickness skin loss involving damage to or necrosis of subcutaneous tissue that may extend down to, but not through, underlying fascia. The ulcer appears as a deep crater with or without undermining of adjacent tissue. Stage 4 pressure ulcers show full-thickness skin loss with extensive destruction, tissue necrosis, or damage to muscle, bone, or supporting structures (e.g., a tendon, joint, or joint capsule). The presence of undermining and sinus tracts (i.e., elongated cavities in which pus may collect) may also be associated with stage 4.

### Treatment

**Nutrition.** Breslow et al.<sup>21</sup> demonstrated the importance of dietary protein in healing pressure ulcers. In this study, malnourished patients who received tube feedings or meal supplements consisting of 24% protein had greater shrinkage in the surface area of the ulcer than patients who received a diet containing 14% protein ( $p < 0.02$ ). Similarly, Chernoff et al.<sup>22</sup> reported that patients who received a 25% protein diet had a higher frequency of ulcer healing or a greater decrease in ulcer size than patients given a 16% protein diet.

The relationship between pressure ulcers and malnutrition is well documented.<sup>23-25</sup> However, maintaining adequate nutrition by itself has not had the same effect on ulcer healing as increased protein intake. One study investigated the effects of enteral feeding on pressure ulcers in 40 patients who were medically dependent on tube feeding for nutrition.<sup>26</sup> Average nutritional requirements for the patients consisted of the Harris-Benedict equation times 1.3 for basal energy expenditure, a mean protein intake of 1.4 g of protein per kilogram per day, and a mean of 104% of the U.S. recommended daily allowance for vitamins and minerals (range, 64–145%). After three months, the number of pressure ulcers was no different from that observed at baseline.

While a deficiency of vitamins and minerals has significant effects on pressure ulcer healing, supplementation remains controversial. A randomized, blinded, multicenter study found no significant difference in the healing of pressure ulcers between 45 patients who received 10 mg of vitamin C twice daily and 43 patients who received 500 mg twice daily.<sup>27</sup> Zinc is known to be essential for wound healing. Studies in animals and humans have shown that supplementation with zinc hastens healing in subjects who are zinc deficient but has no effect on those who are not deficient.<sup>28</sup>

**Wound care.** Before wound care can commence, pressure to the site of the ulcer must be relieved. Furthermore, measures to prevent infection must be taken.<sup>29</sup> For example, it is necessary to debride necrotic tissue. A moist environment, created with a wound dressing, is crucial to maximize healing (Table 1). In cavity wounds, dead space must be filled.

**Debridement.** The purpose of debridement is to reduce the risk of bacterial infection and to aid in healing.<sup>30,31</sup> Four methods of debridement are used, with no single method

preferred over the others. Enzymatic debridement involves the use of a topical agent, such as chlorophyll, papain, or collagenase, to dissolve the necrotic tissue.<sup>31,32</sup> Softening of the eschar with autolysis or cross-hatching (using a sharp instrument to cut lines in the eschar that cross one another at an angle) is typically necessary before applying the enzyme, since dissemination of the enzyme into the eschar is otherwise insufficient. Autolytic debridement involves the use of the enzymes present in the wound to aid in dissolving the devitalized tissue and is accomplished by using a moist wound dressing, such as a hydrocolloid or a hydrogel.<sup>33</sup> Mechanical debridement involves allowing moist gauze to dry and adhere to the tissue prior to removal. This is often painful for the patient and can remove both viable and nonviable tissue.<sup>33</sup> Sharp debridement is a surgical procedure utilizing a scalpel or scissors to remove dead tissue. This can be performed at the bedside or in the operating room, depending on the extent of debridement needed.<sup>33</sup> This method is most commonly indicated if the necrotic tissue is infected.<sup>31</sup>

**Wound dressings.** Skin sealants can be used for stage 1 ulcers or to protect the skin around open wounds.<sup>29</sup> Skin sealants create a protective coating on the patient's skin, acting as a barrier between healthy skin and the topical product that is applied.<sup>34</sup> These are commercially available as ointments, gels, wipes, and sprays.

Hydrogel dressings can be useful in maintaining a moist environment for wounds with little or no exudate (because of their high water content, hydrogels do not absorb large amounts of exudates).<sup>29</sup> These dressings may assist in maintaining a moist wound-healing environment and promoting the natural healing process, since they are insoluble in water but absorb aqueous solutions.<sup>31</sup> This nonadherent type of dressing conforms to the wound bed

Table 1.  
Dressings for Pressure Ulcers

Type of Dressing	Indication	Uses	Disadvantages	Commercially Available Products
Skin sealants	Stage 1 ulcers, skin around open ulcers	Creating a protective coating on the skin, acting as a barrier between healthy skin and topical product	None	Decubitene Oxygenated Oil, Preppies Skin, Pro-Q Skin Protectant
Hydrogels	Ulcers with little or no exudate	Maintaining a moist environment, promoting the wound-healing process, promoting autolytic debridement, reducing pain	May cause tissue maceration around the ulcer, a secondary dressing is necessary, may adhere to the ulcer bed if it dries, may promote growth of organisms	Aqua Skin, Carrasyn V, Woun'Dres
Hydrocolloids	Stage 2 ulcers	Maintaining a moist environment, allowing clean ulcers to heal naturally, promoting autolytic debridement	Cannot be used in the presence of heavy exudate, sinus tracts, ulcers with eschar formation, exposed bones or tendons, third-degree burns, or infections	Comfeel Plus, Curaderm, DuoDerm
Alginates	Exudating stage 2 ulcers; stage 3 or 4 ulcers that are deep, tracking, or undermined or have moderate drainage	Maintaining a moist environment	Should be avoided in third-degree burns, heavily bleeding ulcers, and dry ulcers; may require hydration before removal; a secondary dressing is necessary	Kalginat, Kaltostat, Sorbsan
Foams	Partial-thickness or full-thickness ulcers with moderate to heavy drainage	Repelling water, bacteria, and other contaminants; maintaining a moist environment; acting as insulation; reducing odor	Some patients require a secondary dressing; maceration may occur in surrounding skin; should not be used for dry ulcers, partial-thickness ulcers, ulcers with a small amount of drainage, arterial ischemic lesions, or ulcers with exposed muscle, tendon, or bone	Allevyn, Biatain, Silon
Sodium chloride solution-impregnated gauze	Stage 2, 3, and 4 ulcers	Maintaining a moist environment	Absorbs minimal amounts of exudate, dressing must be removed while still moist, multiple dressing changes per day are required	Curasalt Sodium Chloride Dressing, Dermagran Wet Saline Dressing, Kerlix/Curity Saline Dressing

and promotes autolytic debridement. Further, it can reduce pain by having a cooling and soothing effect. These dressings include water- or glycerin-based gels, impregnated gauzes, and sheet dressings.

Hydrogel dressings have several disadvantages. They may cause maceration of tissue around the wound. For the dressing to be secured, a secondary dressing is necessary. The dressing may dry and adhere to the

wound bed if not changed on a regular basis. Finally, the sheet form may promote growth of organisms because of the moist environment.<sup>34</sup>

Hydrocolloid dressings are useful for shallow, uninfected pressure ul-

cers with small to moderate amounts of exudate, such as clean stage 2 ulcers.<sup>29,35</sup> These dressings are occlusive or semiocclusive, vary in their ability to absorb materials, and adhere to the skin.<sup>31,34</sup> In addition, they are impermeable to water, oxygen, bacteria, and other contaminants.<sup>34</sup> While porous to moisture, hydrocolloid dressings are not porous to water. Thus, they provide a moist environment and allow clean wounds to progress with their natural healing process. Hydrocolloids also facilitate autolytic debridement.<sup>29</sup> This type of dressing may be left in place for up to seven days,<sup>35</sup> thereby minimizing skin trauma and disruption of healing.

Hydrocolloid dressings are cost efficient, are easy to apply, and are available in various sizes and shapes. Typically, they are available as self-adhesive pads, but they also come in paste, powder, and granular forms.<sup>29,34,36</sup> The pastes or granules can be used to fill in a shallow fissure ulcer, and a secondary dressing can then be applied over the ulcer.<sup>35</sup> Hydrocolloid dressings should be avoided in the presence of heavy exudate, sinus tracts, wounds with eschar formation, exposed bones or tendons, third-degree burns, and infections.<sup>29,31</sup>

Dressings designed to absorb moderate to large amounts of exudate include alginates, foams, and saline-impregnated gauze.<sup>29</sup> Alginate dressings, which are derived from brown seaweed, can hold up to 20 times their weight and fill in open spaces. These dressings are useful for exudating stage 2 wounds and for stage 3 or 4 wounds that are deep, tracking, or undermined or that have moderate drainage.<sup>35</sup> Alginates are available in rope, ribbon, and pad forms and require an additional, secondary dressing. Typically, ropes are used to pack hollow areas. Ribbons may be preferred to ropes to pack constricted areas. In a deep wound, pads may be the ideal choice.<sup>34</sup> When packed into a wound, an alginate dressing interacts with the wound

fluids to form a gel. The gel sustains the moist milieu conducive to healing. Removal of an alginate dressing from a wound that has dried out may damage tissue.<sup>31</sup> Alginates should be avoided in third-degree burns, heavily bleeding wounds, and dry wounds.<sup>29</sup>

Foam dressings are made of polyurethane and are absorbent.<sup>29</sup> These products are useful for partial- or full-thickness wounds with moderate to heavy drainage. Foams can repel water, bacteria, and other contaminants<sup>29,34</sup>; create a moist healing environment; and act as insulation. Some products have a charcoal filter integrated into the dressing to reduce odor.<sup>34</sup> Foam dressings are available as sheets of variable thickness with or without adhesive coatings and with or without film coatings on one side. These dressings may require a secondary dressing, tape, or securing device to keep them in place. Foams should be used cautiously, as they may macerate surrounding skin. They should not be used for dry wounds, partial-thickness wounds, wounds with little drainage, arterial ischemic lesions, or wounds with exposed muscle, tendon, or bone.<sup>29,34</sup>

Gauze dressings are cost-effective and easily obtained. When used appropriately, gauze dressings are practical for stage 2, 3, and 4 pressure ulcers.<sup>35</sup> Gauze dressings absorb minimal amounts of exudates. A moist gauze dressing should be applied to the wound, remain hydrated while on the wound, and be removed while still moist. Typically, maintaining a moist environment requires changing a gauze dressing several times a day.

Gauze dressings may be impregnated with additional substances, such as 0.9% sodium chloride solution. These dressings are available in many sizes and forms, including pads, strips, ropes, sponges, tubes, and ribbons.<sup>34</sup> Gauze can also be combined with other topical products or other types of dressings and

can be loosely packed into open wounds.

**Topical growth factors.** Growth factors are peptides that have been found in vivo and in vitro to show promise for tissue repair.<sup>36</sup> Growth factors that have been studied for this purpose include colony-stimulating factor, EGF, PDGF, IGF-I, IGF-II, fibroblast growth factor (FGF), TGF- $\beta$ , IL-1, TNF- $\alpha$ , and nerve growth factor (NGF).<sup>14,36,37</sup> Several human studies have investigated growth factors for use in the treatment of pressure ulcers. To date, no growth factor has received FDA-approved labeling for such use.

**Topical IL-1.** IL-1 encompasses a group of associated proteins. IL-1 $\alpha$  and IL-1 $\beta$  are two proteins with IL-1-like activity encoded by two distinctive complementary DNAs.<sup>37</sup> Both forms have the same biological function and bind to the same type of receptor. Only the effects of IL-1 $\beta$  on tissue repair have been studied in humans. IL-1 $\beta$  has been found to aid in wound healing by chemoattraction of neutrophils and macrophages to the wound site, stimulation of fibroblast production, and stimulation of endothelial cell proliferation.<sup>38-40</sup>

Robson et al.<sup>41</sup> studied the safety and efficacy of three concentrations of recombinant human IL-1 $\beta$  (rhu IL-1 $\beta$ ) for stage 3 and 4 pressure ulcers. In this prospective, randomized, double-blind trial, 24 patients received 28 days of therapy consisting of rhu IL-1 $\beta$  0.01, 0.1, or 1.0  $\mu\text{g}/\text{cm}^2/\text{day}$  or placebo. No significant differences in percent decrease in wound size were observed among the groups. No patient required discontinuation of treatment because of toxicity.

**Topical FGF.** FGF exists in two forms, bFGF and acidic FGF.<sup>36</sup> Both forms have the same effects, although, depending on the targeted cell, bFGF is up to 100 times more potent. The basic form has been more extensively studied. Basic FGF has been found to provoke cell mitogenesis and chemotaxis.<sup>42</sup> In vivo, bFGF prompts neovas-

cularization and causes collagen synthesis.<sup>43</sup> Recombinant human bFGF accelerates wound healing in animals through stimulation of angiogenesis, granulation, wound contraction, and epithelialization.<sup>44,45</sup>

To date, two studies in humans have been published. Robson and colleagues<sup>46</sup> randomized 49 patients with stage 3 or 4 pressure ulcers to receive 100 or 500 µg of bFGF per milliliter at three application schedules, 1000 µg of bFGF per milliliter at two application schedules, or placebo for 13–22 days (the total study period was 30 days). The percent decrease in wound volume did not differ significantly between patients treated with bFGF or placebo. However, 60% of patients who received bFGF had a >70% decrease in wound volume, versus only 29% in the placebo group ( $p = 0.047$ ).

The other human study examined sequential use of granulocyte-macrophage colony-stimulating factor (GM-CSF) and bFGF in hospitalized patients.<sup>47</sup> The authors hypothesized that sequential use of these two agents would result in enhanced ulcer healing, with GM-CSF working in the early stages of wound healing and bFGF in the later stages. Sixty-one patients who had had stage 3 or 4 ulcers for greater than eight weeks were randomized into one of four treatment groups: GM-CSF 2 µg/cm<sup>2</sup> topically daily for 35 days, bFGF 5 µg/cm<sup>2</sup> topically daily for 35 days, GM-CSF 2 µg/cm<sup>2</sup> topically daily for 10 days followed by bFGF 5 µg/cm<sup>2</sup> topically daily for 25 days, and placebo daily for 35 days. Fifteen patients were enrolled in each treatment group, except the GM-CSF and bFGF group, in which 16 patients were enrolled. Although patients treated with bFGF had the lowest ulcer volume (a median of 4.42 cm<sup>3</sup>, compared with 7.48–9.92 cm<sup>3</sup> for the other treatments and placebo) and the highest percentage of wound closure (a median of 79%, versus 70–73%), the differences were not significant. Compared with placebo recipi-

ents, cytokine recipients were significantly more likely to have a more than 85% decrease in ulcer volume ( $p < 0.05$ ). Also, significantly more patients in the bFGF group than the placebo group had greater than 85% wound closure ( $p < 0.05$ ).

**Topical NGF.** NGF was first described in the 1950s.<sup>48</sup> Hypothetically, topical NGF is intended to aid in wound healing by encouraging growth and demarcation of epithelium-derived cells.<sup>37</sup> Topical NGF hastened wound healing in both normal and diabetic mice.<sup>49,50</sup> To date, only one human study has been published. Landi and colleagues<sup>37</sup> studied the efficacy of topical NGF compared with conventional topical treatment in patients with severe, noninfected pressure ulcers of the foot. This randomized, double-blind trial evaluated 18 patients each in the treatment and placebo groups. Treatment consisted of 1 mg of murine NGF dissolved in 20 mL of balanced salt solution and applied to the ulcer daily. Therapy was continued until the wound healed or for a maximum of six weeks. Daily local wound care was provided to both groups. After six weeks, complete healing was documented in 44% and 6% of patients in the NGF and placebo groups, respectively ( $p = 0.009$ ). Improvement in one or more stages was noted in all the NGF recipients but only 55% of the placebo recipients ( $p < 0.001$ ). However, the results of trials in which the control group's healing rate is low should be cautiously interpreted.<sup>48</sup>

**Topical PDGF.** Recombinant human BB platelet-derived growth factor (rPDGF-BB) has been found to stimulate the migration of neutrophils, macrophages, and fibroblasts into wounds; hasten the accumulation of glycosaminoglycans and fibronectin; and enhance collagen production.<sup>51–54</sup> In animal studies, rPDGF-BB generated wound repair effectively. To date, rPDGF-BB is the most extensively studied growth factor for wound healing in humans.

Robson and Phillips<sup>51</sup> randomized 20 hospitalized patients with stage 3 or 4 pressure ulcers to receive rPDGF-BB 1 µg/mL ( $n = 4$ ), 10 µg/mL ( $n = 4$ ), or 100 µg/mL ( $n = 5$ ) or placebo ( $n = 7$ ) topically daily for four weeks. This double-blind, Phase I and II study found that patients treated with rPDGF-BB 100 µg/mL had twice as large a decrease in ulcer depth throughout the treatment period as the other two treatment groups and the placebo recipients ( $p \leq 0.05$ ).

In another trial, patients who had had stage 3 or 4 pressure ulcers for at least two months randomly received 100 or 300 µg of rPDGF-BB per milliliter or placebo daily for 28 days.<sup>55</sup> Forty-one patients completed this Phase II, double-blind, multicenter study (15 patients in the 100-µg/mL treatment group, 12 in the 300-µg/mL treatment group, and 14 in the placebo group). No serious adverse effects of the study drug were observed. Ulcer volume on day 29 was smaller in both treatment groups compared with placebo, but the differences were not significant. A follow-up examination of these patients at five months indicated that the effects of treatment were temporary, since a majority of ulcers remained unhealed.

The largest study to date was a prospective, multicenter, double-blind, parallel-group trial of the commercially available PDGF becaplermin.<sup>56</sup> One hundred twenty-four patients with stage 3 or 4 pressure ulcers were randomized to receive gel containing 100 µg of becaplermin per gram once daily alternating with placebo gel every 12 hours ( $n = 31$ ), 300-µg/g becaplermin gel once daily alternating with placebo gel every 12 hours ( $n = 32$ ), 100-µg/g becaplermin gel twice daily ( $n = 30$ ), or placebo ( $n = 31$ ). Good wound care was also provided to all four treatment groups until the ulcer was completely healed or for a maximum of 16 weeks. Adverse effects were similar in all treatment groups and included

skin ulceration, urinary-tract infection, rash, erythema, and fever. Complete healing was significantly more frequent with 100 or 300 µg of becaplermin per gram once daily than with placebo ( $p = 0.005$  and  $0.008$ , respectively). A significant difference was not observed between the becaplermin 100-µg/g twice daily group and the placebo group. No ulcers in the placebo recipients healed completely, compared with 3% of ulcers in the patients given becaplermin 100 µg/g twice daily, 19% of ulcers in the 300-µg/g once daily group, and 23% of ulcers in the 100-µg/g once daily group. However, interpretation of the results may be confounded by the negative dose-response effect, a substantially lower rate of healing than observed for other standard treatments, and failure of any ulcers to heal in the placebo recipients.<sup>14</sup>

**Human skin equivalents.** Human skin equivalents are thought to be ideal treatments for pressure ulcers, since cell and growth factors are added to an otherwise poor wound-healing environment.<sup>57</sup> FDA has approved the labeling of human skin equivalents for use in the treatment of venous ulcers and full-thickness neuropathic diabetic foot ulcers.<sup>58-60</sup> In a study by Brem and colleagues,<sup>57</sup> 13 patients with pressure ulcers were treated with Apligraf (Organogenesis, Inc.), a living, bilayered skin substitute. All patients were surgically debrided and received alternating air-mattress therapy. Of the 13 patients, 7 experienced wound healing. All wounds were healed with one application of the skin substitute. The current cost of one application of Apligraf is \$1000; studies are needed to compare the efficacy and the cost-effectiveness of this treatment with those of standard therapy.

### Infections in pressure ulcers

**Interpreting culture results.** The presence of bacteria is to be expected in all open wounds within two days.

In acute wounds, particularly those with an ongoing inflammatory component, such colonization appears to be associated with a greater frequency of tissue loss and systemic infection. Bacterial colonization of chronic wounds does not appear to result in the same outcomes and may persist for months with no outward signs of infection.<sup>61</sup> This observation has also been noted for wounds covered with occlusive dressings.<sup>62</sup> Results of cultures and quantitative microbiology testing, in the absence of clinical signs and symptoms of infection, must be carefully interpreted.

Daltrey et al.<sup>63</sup> studied 74 pressure ulcers in 53 geriatric patients to determine the relationship between (1) the type and amount of bacteria present and (2) healing rates. Aerobic cultures were obtained from all patients; anaerobic cultures from 20 patients. Gram-negative bacteria, notably *Pseudomonas aeruginosa* and *Proteus mirabilis*, were associated with 71% of ulcers considered to be nonhealing or worsening, while only 9% of healing ulcers produced gram-negative cultures. Of the 20 anaerobic cultures obtained, 6 were positive and were most frequently associated with necrotic lesions. The authors noted that all anaerobic isolates were concurrently infected by gram-negative bacteria and that necrotic and worsening ulcers were more likely to contain *P. aeruginosa* and *Proteus* species.

Sapico and colleagues<sup>64</sup> assessed 25 pressure ulcers in patients with spinal cord injuries. Specimens from ulcers with significant quantities of necrotic tissue frequently included gram-negative and anaerobic bacteria. In cultures taken from ulcers without obviously necrotic tissue, few anaerobes were isolated, and *P. aeruginosa* and *Staphylococcus aureus* were most prevalent. The authors noted no significant correlation between the culture results and clinical symptoms, including increased white-blood-cell counts and fever.

Rudensky et al.<sup>65</sup> sampled 72 pressure ulcers in 51 patients with three collection techniques (sterile swab, tissue biopsy, and needle aspiration). Forty-three ulcers were evaluated by all three methods. Forty-two (98%) of the swab samples, 27 (63%) of the tissue biopsy samples, and 23 (53%) of the needle aspiration samples yielded positive cultures. There were fewer bacterial species in the samples obtained by needle aspiration than in the samples obtained by the other two methods. *P. aeruginosa* and *P. mirabilis* were the species most commonly identified in all 72 ulcers. The authors concluded that antibiotic therapy should not be initiated on the basis of superficial collection techniques alone.

**Indications for systemic antibiotic therapy.** Osteomyelitis and sepsis secondary to infected pressure ulcers are two indications that warrant the use of systemic antibiotics. Osteomyelitis may result from a contiguous spread of pathogens from an ulcer and is thought to delay the ability of the overlying wound to heal. In several studies assessing pressure ulcers for the presence of underlying osteomyelitis, osteomyelitis had been diagnosed in 17–66% of the cases.<sup>66-68</sup>

Galpin et al.<sup>69</sup> evaluated the medical records of 21 patients diagnosed with sepsis attributed to pressure ulcers. Sixteen of the 21 patients were bacteremic. Cultures were classified as aerobic (6 patients), anaerobic (7), and mixed (3). The organisms most commonly isolated from the ulcers of all patients were *Proteus* species, group D streptococci, and *Escherichia coli*, while *Bacteroides fragilis*, *P. mirabilis*, and *Peptococcus* and *Peptostreptococcus* species were most frequently isolated from the blood. All patients were treated with empirical antibiotic regimens. Fourteen patients also underwent surgical debridement. Ten patients subsequently died.

Bryan and colleagues<sup>70</sup> studied the medical records of 102 patients to establish the frequency of bacteremia

associated with pressure ulcers. The authors considered pressure ulcers to be the probable source of infection on the basis of physician or nursing documentation in the medical chart, correlation of blood and ulcer culture results, or documentation of osteomyelitis. In 51 cases, pressure ulcers were deemed the probable source of bacteremia. The authors noted that, in 86% of the study population, a secondary source of infection was also documented. *P. mirabilis*, *S. aureus*, and *Bacteroides* species were most commonly isolated from blood cultures of patients in the "probable" group. Antibiotic therapy was deemed appropriate on the basis of in vitro bacterial susceptibility and inappropriate if the organisms were not susceptible. The rate of mortality secondary to bacteremia in the probable group was 31%. The mortality difference between the appropriate and inappropriate antibiotic therapy treatment groups approached significance ( $p = 0.056$ ). The authors concluded that pressure ulcers may be an underrecognized cause of bacteremia.

**Topical antimicrobial therapy.** In addition to vigilant wound care, topical antimicrobial agents are frequently used to treat pressure ulcers. To date, three topical antimicrobial therapies have been studied in patients with pressure ulcers: gentamicin, silver sulfadiazine, and metronidazole. In one study, 20 patients with a total of 31 pressure ulcers were randomly assigned to a standard treatment regimen or standard treatment plus 0.1% gentamicin cream applied topically three times daily.<sup>71</sup> The two groups were demographically dissimilar, with the average age of patients in the standard therapy group being 80 years, versus 60 years in the gentamicin group. The authors reported a significant improvement in the clinical response of the ulcers in the gentamicin group compared with the recipients of standard therapy alone, along with a direct and significant correlation between clinical

response and bacterial counts. It was concluded that the addition of gentamicin and the resulting decrease in bacterial load contributed to the healing of pressure ulcers.

Kucan and colleagues<sup>72</sup> studied the effects of topical 1% silver sulfadiazine, povidone-iodine, and 0.9% sodium chloride solution in hospitalized patients. Outcome measures included a decrease in bacterial load and clinical improvement. Systemic antibiotic therapy was permitted for patients developing additional infections and did not differ significantly among the three treatment groups. Patients in the 1% silver sulfadiazine group ( $n = 15$ ) were significantly more likely to achieve a reduction in bacterial counts and an improved clinical response than patients in the povidone-iodine group ( $n = 11$ ) ( $p \leq 0.022$  and  $p < 0.01$ , respectively) but not patients in the 0.9% sodium chloride solution group ( $n = 14$ ) ( $p$  not reported and  $p < 0.10$ , respectively).

The use of topical metronidazole for the treatment of infected pressure ulcers has been reported. Gomolin and Brandt<sup>73</sup> studied a self-compounded preparation in four patients with stage 2-4 ulcers. Although culture results were not obtained, assessment of odor and appearance led the authors to conclude that the treated ulcers were infected, presumably with anaerobic bacteria. A 1% metronidazole solution was prepared and applied to sterile gauze, which was covered with a protective layer. The dressings were applied every eight hours. Odor and drainage decreased and granulation tissue appeared in all four patients. The authors noted that, in two other patients, the application of topical metronidazole to ulcers in the same stages but without odor, drainage, or necrotic tissue failed to produce any improvement. No systemic or local adverse effects of metronidazole were observed.

In a study by Witkowski and Parish,<sup>74</sup> a commercially available

metronidazole gel was used to treat 10 foul-smelling stage 3 or 4 pressure ulcers. All 10 patients were undergoing systemic antibiotic therapy for other conditions at the time of this study. Culture results were obtained for all the ulcers. While all the ulcers contained aerobic bacteria, *Bacteroides* species was isolated from only 5 of the 10 patients. Standard wound care, including removal of necrotic material and irrigation with 0.9% sodium chloride solution, preceded metronidazole therapy. Metronidazole gel was applied to each ulcer every 12 hours, and the wound was loosely packed with gauze that was secured with a protective covering. In each case, the foul odor disappeared within 36 hours of treatment. A decrease in drainage and necrotic tissue and the appearance of granulation tissue were also noted. Repeat cultures obtained five days after treatment demonstrated no anaerobic growth. Aerobic organisms remained in all ulcers. The authors concluded that topical metronidazole gel was effective in eliminating anaerobic bacteria and foul odor from infected pressure ulcers.

## Conclusion

No pharmacologic intervention has been conclusively shown to be effective for pressure ulcers. The cornerstones of therapy remain elimination of the source of pressure or friction and appropriate wound care.

## References

1. Dealey C. Review of advances in pressure ulcer management since 1992. *Br J Nurs*. 2002; 11:486-90.
2. Xakellis GC, Frantz RA. The cost-effectiveness of interventions for preventing pressure ulcers. *J Am Board Fam Pract*. 1996; 9(2):79-85.
3. Kerstein MD. Unexpected economics of ulcer care protocols. *South Med J*. 2004; 97:135-6.
4. Gallagher S. Outcomes in clinical practice: pressure ulcer prevalence and incidence studies. *Ostomy Wound Manag*. 1997; 43:28-32,34-5,38.
5. Wysocki AB. Skin anatomy, physiology, and pathophysiology. *Nurs Clin North Am*. 1999; 34:777-97.

6. Burkitt HG, Young B, Heath JW. Wheat-er's functional histology: a text and colour atlas. Edinburgh, Scotland: Churchill Livingstone; 1993.
7. Wysocki AB. A review of the skin and its appendages. *Adv Wound Care*. 1995; 8(2, part 1):53-4,56-62,64.
8. Goldsmith LA. Physiology, biochemistry, and molecular biology of the skin. New York: Oxford Univ. Press; 1991.
9. Mast BA, Schultz GS. Interactions of cyto- kines, growth factors, and proteases in acute and chronic wounds. *Wound Re- pair Regen*. 1996; 4:411-20.
10. Goldman R. Growth factors and chronic wound healing: past, present, and future. *Adv Skin Wound Care*. 2004; 17(1):24-35.
11. Mauch C, Kreig T, Bauer RA. Role of the extracellular matrix in the degradation of connective tissue. *Arch Dermatol Res*. 1994; 287:107-14.
12. Hunt TK. Basic principles of wound heal- ing. *J Trauma*. 1990; 30:122s-8s.
13. Meehan M. National pressure ulcer prev- alence survey. *Adv Wound Care*. 1994; 7(3):27-30,34,36-8.
14. Thomas DR. Age-related changes in wound healing. *Drugs Aging*. 2001; 18: 607-20.
15. Patterson JA, Bennett RG. Prevention and treatment of pressure sores. *J Am Geriatr Soc*. 1995; 43:919-27.
16. Schouchoff B. Pressure ulcer develop- ment in the operating room. *Crit Care Nurs Q*. 2002; 25(1):76-82.
17. Alessi CA, Ouslander JG, Maldague S et al. Incidence and costs of acute medical conditions in long-stay incontinent nurs- ing home residents. *J Am Med Dir Assoc*. 2003; 4:S5-18.
18. Allman RM. Pressure ulcers among the elderly. *N Engl J Med*. 1989; 320:850-3.
19. Higley HR, Ksander GA, Gerhardt CO et al. Extravasation of macromolecules and possible trapping of transforming growth factor-beta in venous ulceration. *Br J Dermatol*. 1995; 132:79-85.
20. National Pressure Ulcer Advisory Panel. Staging report. [www.npuap.org/ positn6.html](http://www.npuap.org/positn6.html) (accessed 2004 Feb 17).
21. Breslow RA, Hallfrisch J, Guy DG et al. The importance of dietary protein in healing pressure ulcers. *J Am Geriatr Soc*. 1993; 41:357-62.
22. Chernoff RS, Milton KY, Lipschitz DA. The effect of a high protein formulation (Replete) on decubitus ulcer healing in long term tube fed institutionalized pa- tients. *J Am Diet Assoc*. 1990; 90:A-130.
23. Pinchcofsky-Devin GD, Kaminski MV. Correlation of pressure sores and nutri- tional status. *J Am Geriatr Soc*. 1996; 34: 435-40.
24. Bergstrom N, Braden B. A prospective study of pressure sore risk among institu- tionalized elderly. *J Am Geriatr Soc*. 1992; 40:747-58.
25. Berlowitz DR, Wilking SV. Risk factors for pressure sores. A comparison of cross- sectional and cohort-derived data. *J Am Geriatr Soc*. 1989; 37:1043-50.
26. Henderson CT, Trumbore LS, Mobarhan S et al. Prolonged tube feeding in long- term care: nutritional status and clinical outcomes. *J Am Coll Nutr*. 1992; 11:309-25.
27. Ter Riet G, Kessels AH, Knipschild PG. Randomized clinical trial of ascorbic acid in the treatment of pressure ulcers. *J Clin Epidemiol*. 1995; 48:1453-60.
28. Sandstead HH, Henriksen LK, Greger JL et al. Zinc nutriture in the elderly in rela- tion to taste acuity, immune response, and wound healing. *Am J Clin Nutr*. 1982; 36:1046-59.
29. Calianno C. How to choose the right treatment and dressing for the wound. *Nurs Manag*. 2003; 34(1):6-14.
30. Constantine BE, Bolton LL. A wound model for ischemic ulcers in the guinea pig. *Arch Dermatol Res*. 1986; 278:429-31.
31. Thomas DR. Prevention and treatment of pressure ulcers: what works? What doesn't. *Cleve Clin J Med*. 2001; 68:704-22.
32. Wound care information network: types of wound debridement. [www. medicaledu.com/debridhp.htm](http://www.medicaledu.com/debridhp.htm) (ac- cessed 2004 Feb 19).
33. Wound procedures: debridement. [www. w o u n d s 1 . c o m / c a r e / procedure20.cfm/13](http://www.wounds1.com/care/procedure20.cfm/13) (accessed 2004 Feb 19).
34. Wound care strategies. Consumer's cor- ner. Definitions, products, and manufac- turers. [www.woundcarestrategies.com/ top.htm](http://www.woundcarestrategies.com/top.htm) (accessed 2004 Feb 17).
35. Walker D. Back to basics: choosing the correct wound dressing. *Am J Nurs*. 1996; 96(9):35-9.
36. Rothe M, Falanga V. Growth factors. *Arch Dermatol*. 1989; 125:1390-8.
37. Landi F, Aloe L, Russo A et al. Topical treatment of pressure ulcers with nerve growth factor: a randomized clinical trial. *Ann Intern Med*. 2003; 139:635-41.
38. Dinarello CA, Cannon JG, Mier JW et al. Multiple biological activities of human recombinant interleukin 1. *J Clin Invest*. 1986; 77:1734-9.
39. Dinarello CA. Interleukin-1. *Rev Infect Dis*. 1984; 6(1):51-95.
40. Kaushansky K, Lin N, Adamson JW. In- terleukin 1 stimulates fibroblasts to syn- thesize granulocyte-macrophage and granulocyte colony-stimulating factors. *J Clin Invest*. 1988; 81:92-7.
41. Robson MC, Abdullah A, Burns BF et al. Safety and effect of topical recombinant human interleukin-1 $\beta$  in the manage- ment of pressure sores. *Wound Rep Regen*. 1994; 2:177-81.
42. Gospodarowicz D, Ferrara N, Schweigerer et al. Structural characterization and bio- logical functions of fibroblast growth fac- tor. *Endocr Rev*. 1987; 8(2):95-114.
43. Rifkin DB, Moscatelli D. Recent develop- ments in the cell biology of basic fibro- blast growth factor. *J Cell Biol*. 1989; 109:1-6.
44. Hebda PA, Klingbeil CK, Abraham JA et al. Basic fibroblast growth factor stimula- tion of epidermal wound healing in pigs. *J Invest Dermatol*. 1990; 95:626-31.
45. Fiddes JC, Hebda PA, Hayward P. Pre- clinical wound-healing studies with re- combinant human basic fibroblast growth factor. *Ann N Y Acad Sci*. 1991; 638:316-28.
46. Robson M, Phillips LG, Lawrence WT. The safety and effect of topically applied recombinant basic fibroblast growth fac- tor on the healing of chronic pressure sores. *Ann Surg*. 1992; 216:401-6.
47. Robson MC, Hill DP, Smith PD. Sequen- tial cytokine therapy for pressure ulcers: clinical and mechanistic response. *Ann Surg*. 2000; 231:600-11.
48. Thomas DR. The promise of topical growth factors in healing pressure ul- cers. *Ann Intern Med*. 2003; 139:694-5. Editorial.
49. Matsuda H, Koyama H, Sato H et al. Role of nerve growth factor in cutaneous wound healing: accelerating effects in normal and healing-impaired diabetic mice. *J Exp Med*. 1998; 187:297-306.
50. Li AK, Koroly AJ, Schattenkerk ME. Nerve growth factor: acceleration of the rate of wound healing in mice. *Proc Natl Acad Sci U S A*. 1980; 77:4379-81.
51. Robson MC, Phillips LG. Platelet-derived growth factor BB for the treatment of chronic pressure ulcers. *Lancet*. 1992; 339:23-5.
52. Pierce GF, Mustoe TA, Altrock BW et al. Role of platelet-derived growth factor in wound healing. *J Cell Biol*. 1991; 45:319-26.
53. Deuel TF, Senior RM, Huang JS et al. Chemotaxis of monocytes and neutro- phils to platelet-derived growth factor. *J Clin Invest*. 1982; 69:1046-9.
54. Tzeng DY, Deuel TF, Huang JS et al. Platelet-derived growth factor promotes human peripheral monocyte activation. *Blood*. 1985; 66:179-83.
55. Mustoe TA, Cutler NR, Allman RM et al. A Phase II study to evaluate recombinant platelet-derived growth factor-BB in the treatment of stage 3 and 4 pressure ulcers. *Arch Surg*. 1994; 129:213-9.
56. Rees RS, Robson MC, Smiell JM et al. Becaplermin gel in the treatment of pres- sure ulcers: a Phase II randomized, double-blind, placebo-controlled study. *Wound Rep Regen*. 1999; 7:141-7.
57. Brem H, Balledux J, Bloom T et al. Heal- ing of diabetic foot ulcers and pressure ulcers with human skin equivalent: a new paradigm in wound healing. *Arch Surg*. 2000; 135:627-34.
58. Bello Y, Phillips TJ. Recent advances in wound healing. *JAMA*. 2000; 283:716-8.
59. Apligraf product information. East Hanover, NJ: Novartis Pharmaceutical Corporation; 2002 Feb.
60. Dermagraft product information. [http:// wound.smith-nephew.com/US/ Product.asp?NodeId=2550](http://wound.smith-nephew.com/US/Product.asp?NodeId=2550) (accessed 2004 Feb 19).
61. Thomson PD, Smith DJ. What is infec- tion? *Am J Surg*. 1994; 167(1A):7S-11S.
62. Hutchinson JJ, Lawrence JC. Wound in- fection under occlusive dressings. *J Hosp Infect*. 1991; 17:83-94.

63. Daltrey DC, Rhodes B, Chattwood JG. Investigation into the microbial flora of healing and non-healing decubitus ulcers. *J Clin Pathol.* 1981; 34:701-5.
64. Sapico FL, Ginunas VJ, Thornhill-Jones M et al. Quantitative microbiology of pressure sores in different stages of healing. *Diagn Microbiol Infect Dis.* 1986; 5:31-8.
65. Rudensky B, Lipschits M, Isaacsohn M et al. Infected pressure sores: comparison of methods for bacterial identification. *South Med J.* 1992; 85:901-3.
66. Sugarman B, Hawes S, Musher DM et al. Osteomyelitis beneath pressure sores. *Arch Intern Med.* 1983; 143:683-8.
67. Thornhill-Joyes M, Gonzales D, Stewart CA et al. Osteomyelitis associated with pressure ulcers. *Arch Phys Med Rehabil.* 1986; 67:314-8.
68. Darouiche RO, Landon GC, Klima M et al. Osteomyelitis associated with pressure sores. *Arch Intern Med.* 1994; 154:753-8.
69. Galpin JE, Chow AW, Bayer AS et al. Sepsis associated with decubitus ulcers. *Am J Med.* 1976; 61:346-50.
70. Bryan CS, Dew CE, Reynolds KL. Bacteremia associated with decubitus ulcers. *Arch Intern Med.* 1983; 143:2093-5.
71. Bendy RH, Nuccio PA, Wolfe E et al. Relationship of quantitative wound bacterial counts to healing of decubiti: effect of topical gentamicin. *Antimicrob Agents Chemother.* 1964; 4:147-55.
72. Kucan JO, Robson MC, Hegggers JP et al. Comparison of silver sulfadiazine, povidone-iodine and physiologic saline in the treatment of chronic pressure ulcers. *J Am Geriatr Soc.* 1981; 29:232-5.
73. Gomolin IH, Brandt JL. Topical metronidazole therapy for pressure sores of geriatric patients. *J Am Geriatr Soc.* 1983; 31:710-2.
74. Witkowski JA, Parish LC. Topical metronidazole gel. The bacteriology of decubitus ulcers. *Int J Dermatol.* 1991; 30:660-1.